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From an Editorial in
THE LANCET (August 8, 1931)

"BRIGHT'S method, his great legacy to medical science, was the explanation of disease by a reference to morbid anatomy. This is the ideal which the authors of an important monograph* recently published have set before themselves. It contains the result of a combined investigation by a physician, Prof. THOMAS ADDIS, and a pathologist, Prof. JEAN OLIVER, of 72 cases of Bright's disease in an attempt to correlate the clinical manifestations of the disease with the structural alterations occurring in the kidney. Impressed, as many others have been, by the relative failure of the study of renal function to solve the problems of nephritis, the authors have eschewed all but the simplest functional tests and have relied for their diagnosis of the clinical condition of the patient on the case history, the physical examination, and study of the urinary deposit. Prof. ADDIS has already shown how illuminating the study by an expert of the urinary deposit may be, and in the present work he constantly emphasizes its importance. He insists that the clinical intuition which is so important in other branches of medical practice constantly fails when applied to the complex condition known as Bright's disease so that even masters of the art are frequently misled.

"The pathological side of the investigation, carried out by Prof. OLIVER, has been strictly limited to the examination of the diseased kidney itself, for the renal lesion in Bright's disease was the subject of the investigation, and, moreover, in many cases only the kidneys were available for study. Inasmuch as the clinician considered both the nature and the extent of the renal lesion, it might be expected that the pathologist would do the same, but, as Prof. OLIVER points out, such a procedure at the present time is practically impossible.

"As the result of his observations Prof. ADDIS has arrived at the following classification of Bright's disease: hæmorrhagic Bright's disease, of which the initial, latent, active, and terminal stages can be recognised; degenerative Bright's disease, including the cryptic, pyogenic, non-bacterial, and bacterial forms; and arteriosclerotic Bright's disease; and the cases are grouped under these headings. The history and relevant clinical details of each case are given at length, and there is a brief description of the naked-eye appearances of the kidneys and a detailed report on their microscopic structure. But the feature of the case records are the illustrations—the structure of each kidney is illustrated by two photomicrographs, one of a magnification of 20, the other of 125, so that the reader is able to see for himself the actual lesion associated with the clinical condition described. There are 142 of these plates, and they are admirably reproduced—the lower magnifications are sometimes a little difficult, but with careful study they will be found to fulfil the purpose claimed for them. These plates are not illustrations in the ordinary sense of the term; they 'were not chosen to elucidate the text, but rather the text supplements, in its insufficient way, the actual images, as near as may be, which we had before us in our study.' There are, however, in addition, 26 high-power drawings of frankly selected specimens chosen to illustrate the text. The book is concluded by short chapters summarising and correlating the clinical and pathological data."

"It would be almost impertinent to offer praise to such an admirable example of what can be achieved, without dogmatism or bias, to clarify one of the most complicated problems in medicine.

[Complete Editorial from The Lancet is too long for reproduction here. It will be sent on request]

*THE RENAL LESION IN BRIGHT'S DISEASE

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The Vital Hormone of the Adrenal Cortex*†

By Frank A. Hartman, A.M.,Ph.D.; Byron D. Bowen, M.D., F.A.C.P.; Geo. W. Thorn, M.D., and Clayton W. Greene, M.D., F.A.C.P.

IT HAS been known for many years that the adrenal glands are essential to life; but Wheeler and Vincent were the first to prove, at least in mammals, that the medulla was not essential. They found that as long as an adequate amount of cortex survived, destruction of all of the medullary tissue led to no ill effects.

The next step in the study of the cortex was the preparation of an extract containing the hormone. The cortex contains a sufficient amount of epinephrin to make the removal of the latter necessary, especially if the extract is to be concentrated.

In October, 1927, Rogoff and Stewart described the results obtained with two preparations; one a simple 0.9 per cent NaCl extract and the other a glycerol extract of the cortex. These methods do not eliminate the epinephrin and therefore definitely limit the amount of material which can be injected, on account of the epinephrin content of the extracts produced. Their report did not give the average survival of treated animals as compared with controls, although of thirty dogs treated, six lived longer than the longest of the control animals.

In the same month Hartman, MacArthur and Hartman described a method for preparing an epinephrin-free cortical extract. With such an extract it was possible to increase markedly the survival period of completely adrenalectomized cats, the average survival period of all of the treated animals being twenty-one days as compared with six days for the untreated animals.

In March, 1930, Swingle and Pfiffner described a method of preparing a concentrated extract sufficiently potent to maintain the lives of adrenalectomized cats indefinitely. Their extract contained much epinephrin and inert material and was prepared by a long and complicated process.

In June, 1930, Hartman and Brownell described a simpler process for the preparation of a concentrated cortical extract. Their extract, containing less than 1:100,000 epinephrin, could be administered intravenously as well as subcutaneously. One patient has been injected subcutaneously four times daily for more than seven months without untoward results.

Experiments on animals have served as a basis for clinical work; therefore an outline of these results should precede the clinical studies.

*From the Departments of Physiology and of Medicine, University of Buffalo, Buffalo, N. Y.

†Presented at the Baltimore meeting of the American College of Physicians, March 26, 1931.

Animal Experiments

With the concentrated extract it is possible not only to maintain the lives of adrenalectomized animals indefinitely, but to enable such animals to live an apparently healthy existence (figure 1). One completely adrenalectomized cat was kept alive for 268 days and died because the extract was discontinued. Others have been kept alive for more than 150 days. This substance in the cortex which is essential to life has been called cortin.

Adrenalectomized cats treated with adequate cortin, eat well, gain in weight, play and fight. One female "came in heat" and became pregnant. The amount of extract required varies with the individual animal and also depends upon the stresses to which he is subjected. Until recently, in experimental work upon cats, the adrenals have been removed in two stages a few days apart, because if both adrenals were removed at one operation the animal failed to make a good recovery and died in a few days. Now it is possible to remove both adrenals at one operation with excellent recovery if cortin is administered frequently. Such animals will apparently live indefinitely but they require much more cortin at least for a few weeks than those of the two-stage operation. We have removed both adrenals at one operation in three cats. At first the extract was given four times a day following bilateral adrenalectomy, then three times a day. The animals ate well and made a better recovery than many animals subjected to major operations not involving the adrenals. The

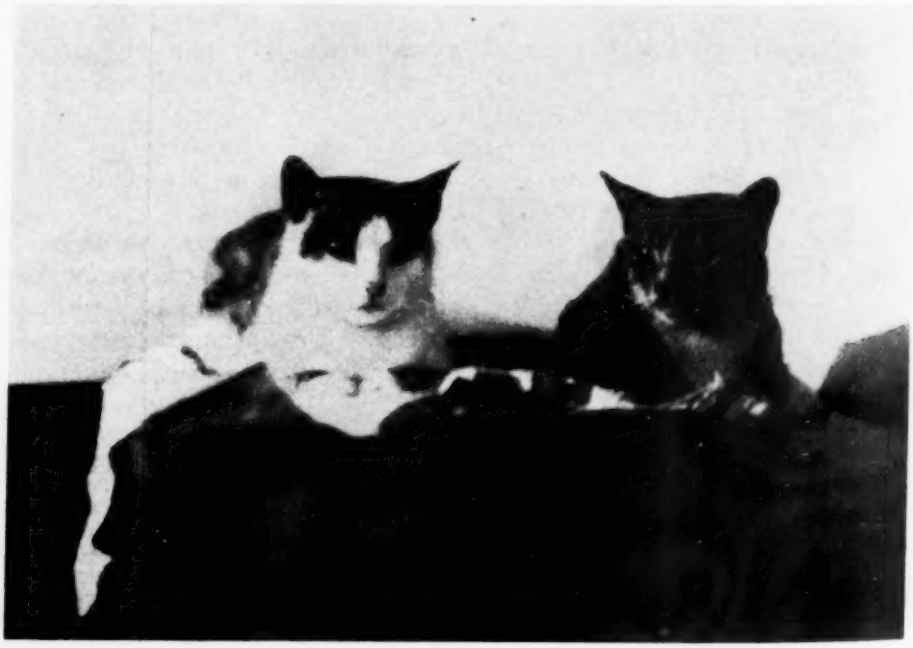

Fig. 1. Completely adrenalectomized cats kept in good condition by cortin.

reduction of extract caused loss of appetite and bloody feces in two, and bloody urine in the third. Increasing the extract caused complete recovery in all cases.

So far it has been impossible to produce overdosage phenomena.

By the administration of cortin one can revive adrenalectomized cats allowed to pass into the last stages of insufficiency preceding death. If the injections are intraperitoneal the effects begin to appear in less than an hour. If given subcutaneously it takes somewhat longer. One animal was allowed to go until there was marked prostration, dyspnea and muscular twitching. Intraperitoneal injection of cortin caused the disappearance of twitching and dyspnea within an hour; ten minutes later she was sitting up; forty minutes later she was eating. Recovery was complete.

Cortin appears to be essential for growth. If both adrenals are removed from young rats, a few continue to grow normally, some grow more slowly and others fail to grow at all, finally dying after days or weeks. Young adrenalectomized rats which are injected with adequate cortin all grow at about the normal rate. The females become pregnant and raise litters; then if the cortin is discontinued, some lose weight and die.

The operative wounds of adrenalectomy and other traumata heal slowly if an insufficient amount of cortin is administered, but they heal normally if an adequate amount is given.

Cortin raises the resistance of adrenalectomized rats to bacterial toxins (Hartman and Scott, Perla and Marmorston-Gottesman). Seventy per cent of the adrenalectomized rats injected with cortin survived a single dose of typhoid vaccine which killed all unprotected adrenalectomized rats. Cortin also protected adrenalectomized rats against increasing dosages of dead *Staphylococcus aureus*. The dosage had reached ten billions per day on the ninth day. At that time sixty per cent of the unprotected rats had died while all the treated ones were still alive and in fairly good condition.

Adrenalectomized animals are very sensitive to cold. When treated with an adequate amount of cortin, they resist cold almost as well as do normals. Two series of completely adrenalectomized rats of 20 and 19 rats respectively were exposed to a temperature which began at 56°F. and gradually fell to 47°F. in ten hours. One series had been injected twice daily with cortin, while the other series had been injected with the same volume of isotonic NaCl solution. Six normal rats were used as controls. Six hours after exposure to cold the average temperature (rectal) of the cortin-treated adrenalectomized rats was almost the same as that of the normals (98.8°F.), while the average temperature of the NaCl-treated adrenalectomized rats was 91.8°F., excluding one that died. At the end of ten hours three more NaCl-treated rats had died while the average temperature of the remaining rats had fallen to 80.9° F. The temperature of the cortin-treated rats had fallen to 95.7°F. as compared with 98.5°F. for the normals.

The poor resistance to cold seems to be due to the inability to produce heat. We have been able to show that rats produce from 10 to 25 per cent less

heat after adrenalectomy. If, however, cortin is administered, heat production is maintained at almost normal levels.

The reduced heat production and lowered resistance to bacterial toxins are probably not specific but are merely manifestations of the reduced activity on the part of the body cells generally.

Clinical Studies

Since asthenia is one of the important manifestations of adrenal insufficiency, we have sought for a method of measuring it in the human.

Ergometer Test for Fatigue. In asthenia there is increased susceptibility to fatigue, although the muscular dynamic power may not decrease materially. Therefore, the measurement of asthenia should test the threshold for fatigue rather than the strength of a single contraction. An ergometer can be used successfully to measure the fatigue threshold, provided certain precautions are observed.

The middle finger lifts weights swung by a chain over a pulley. The adjoining fingers on each side are supported in metal tubes, while the hand is supported on a pad and held in place by a strap over the wrist. The working finger is connected to the chain by a leather thong or stall. The finger lifts the weight at every other beat of a metronome which is beating seconds. This is continued until the finger definitely fails to lift the weight up to a given mark. This end point is important and can be determined best by an experienced operator. The load chosen should be one that causes fatigue in from three to five minutes. If too heavy, the error due to variation from one test to another may be too large. If too light, the time required for the test is too long, in case marked improvement is subsequently shown. By not making tests too often improvement that might be brought about by training is avoided. The measure of fatigue is the work done (weight x vertical distance raised x number of contractions).

There seems to be less variation in the base level for fatigue in asthenic individuals than in some normal individuals.

For many years numerous workers have endeavored to relieve the symptoms of Addison's disease by the use of adrenal preparations. The earlier efforts have been without notable success, except that the Muirhead treatment has been somewhat effective in cases that were apparently not too severe. Within the past two years three groups of investigators have studied the effects of extracts of the adrenal cortex on clinical cases. Rogoff and Stewart in 1929 treated several patients with an extract administered by mouth. Improvement in symptoms occurred after several weeks of treatment. None of the cases reported seemed to be severe. In January, 1931, Rowntree, Greene, Swingle and Pfiffner reported their results in a number of cases of Addison's disease in which the extract prepared by Swingle and Pfiffner was administered subcutaneously or intravenously. The majority of their cases were benefitted definitely. So far as we have been able to discover, no case has been treated in which there was complete or nearly complete adrenal insufficiency. We wish to report the results of treatment

in two cases of practically complete bilateral atrophy of the adrenal cortex and in a third case in which there appeared to be adrenal insufficiency of lesser degree.

Case 1. A man of 24, a handy-man doing outdoor work for a gas company, was an athlete, specializing in basketball and baseball. In the winter of 1929-30 he noted fatigue in the evening, and he experienced gastro-intestinal upsets. These consisted of anorexia, nausea, and vomiting; and occurred with increasing severity and frequency during the succeeding spring and early summer. In his previous history the only incident had been a febrile attack in 1928, which he said his family physician had diagnosed as "scarlet fever without the rash". Just previous to admission he had been ill for six weeks, showing weakness, epigastric distress, nausea, vomiting, and a loss of thirty to forty pounds in weight since the preceding winter. Upon admission to the hospital July 7, 1930, he was in a state of "collapse", irrational and nearly comatose (figure 2). His systolic blood pressure was 50 mm. and his diastolic was 20 mm.

FIG. 2. Case 1 three days after admission to hospital.

During the first twenty-four hours he received injections of salt solution, glucose and adrenalin subcutaneously, but was not improved. His legs twitched and his extremities were cold. During the second day he received the extract of 3200 grams of adrenal cortex which was given fractionally by frequent subcutaneous injections. On the third day he ate for the first time, seemed more alert, read a little, and did not sleep so much. The daily dose was then reduced to the equivalent of 500 grams of cortex. Gradual improvement took place (figure 3) and the extract was diminished but on the twelfth day he had another relapse when he became almost as ill as he was upon admission. This relapse was occasioned by a further reduction in the extract. A second very severe case (Case 2) was admitted to the hospital at this time and it became necessary to divide the very limited supply of extract between the two, Case 1 receiving the larger portion. A large increase in the amount of extract brought his condition back to its former level of improvement (figure 4). Three subsequent relapses occurred, on the 55th,

FIG. 3. Case 1 six days after beginning cortin.

86th, and 110th days after the institution of treatment. Each was caused apparently by a reduction of the amount of extract. It appeared from clinical observation that the daily administration of the extract from 1000 to 1200 grams of cortex was necessary to prevent the recurrence of symptoms. Also it seemed that injections every six hours were more effective than dosages fifty per cent greater given every eight hours.

It is probable that the amount of cortical hormone needed to obtain improvement in complete adrenal insufficiency, such as Case 1 represents, is much greater than that required for less severe cases such as have been reported from other clinics. In consequence, any question of potency of cortical extracts should be postponed until trial can be made on similar or the same cases. Our dosage has been based upon grams of fresh cortex. Our present extract contains in each cubic centimeter the product obtained from fifty grams of fresh material, although the earlier extract used in the first weeks in Case 1 represented fifteen grams per c. c. When the extract was discontinued it required about three days for the recurrence of nausea, vomiting and asthenia; likewise about three days were necessary for complete recovery to the former level of improvement after the readministration of the extract. This cycle corresponds to the observations on adrenalectomized animals that are treated with the extract.

The blood pressure ranged from 85 to 100 systolic except during the relapses when it fell varying degrees. The temperature was usually about 97.0° F. The blood urea which was 120 mgm. on admission, fell promptly under treatment, but always rose when insufficient extract was given; while the blood sugar fluctuated considerably, reaching the low point, about 75 mgm., during relapses (figure 5).

During the first six and one-half months of treatment his clinical condition remained unchanged except for the short periods of relapse. The pigmentation, however, increased very decidedly. His appetite, weight, and ability to work on the ergometer without fatigue remained about constant. From this time on he made further improvement. On the 224th day he could do six times more work than at the initial test on the ergometer, he had gained ten pounds in weight, his appetite had increased and he volunteered the information, "I can now walk quite fast." Data on the findings and the progress in this case are shown in the accompanying chart. The gaps indicate periods when he returned to his home in a nearby town. During these times he gave himself the injections. His first return to the hospital was because of a relapse, the second was for further study. His basal metabolism varied from minus 7 per cent to minus 15 per cent. While under observation in the hospital, after being out for a few hours one evening, he developed an upper respiratory infection, which persisted for seven days, with slight fever the first day. On the eighth day he had a chill, vomited and his temperature rose to 105.0° F. It was quite obvious that he had had an extension of his respiratory infection. His leucocytes were 30,000 with 84 per cent polymorphonuclears. The extract was

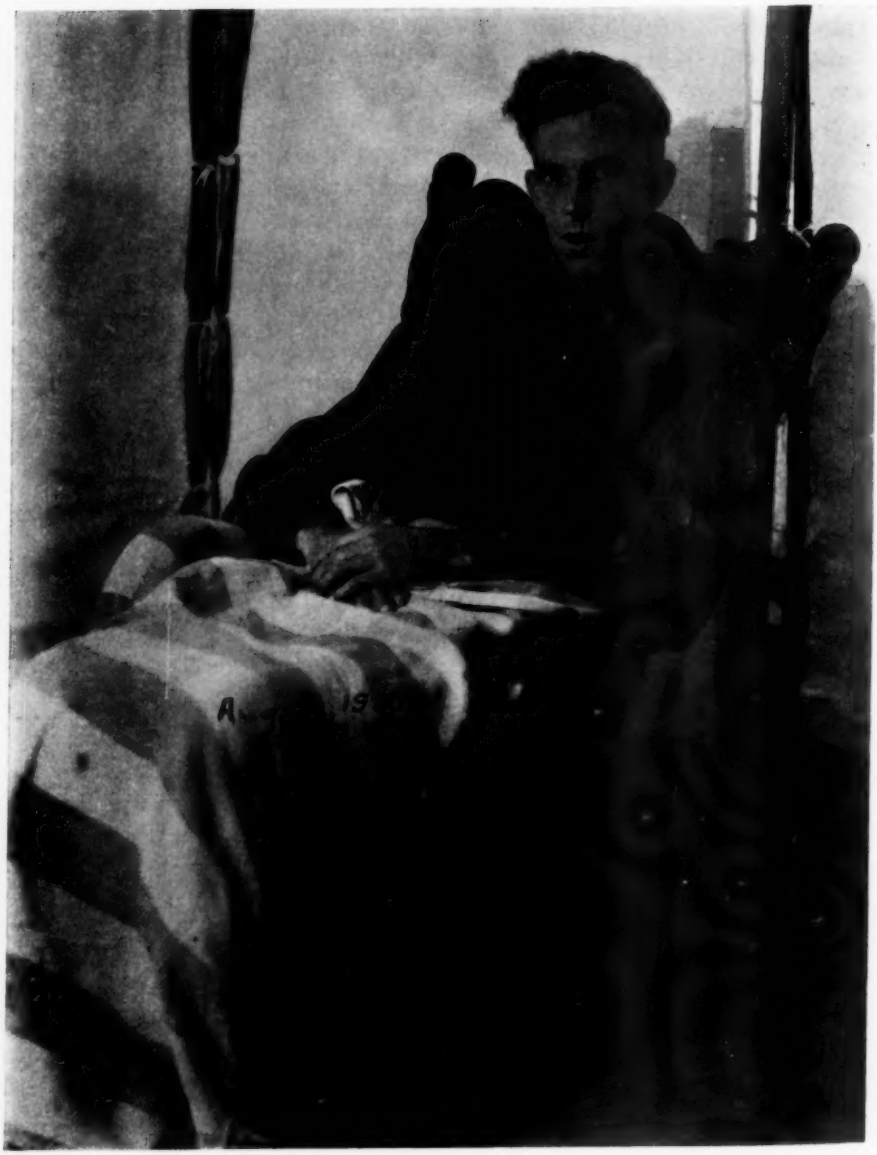

FIG. 4. Case 1 forty-five days after beginning cortin.

increased to the limit available but he died in twenty-four hours.

Autopsy Findings. (A detailed report of the autopsy findings is to appear in Endocrinology). Addison's disease with marked atrophy of both adrenals; weight 3.44 gms. Old calcified tuberculosis of the mesenteric lymph-glands, and fresh tuberculous hyperplasia of a few mesenteric, and especially periaortic, periportal and peripancreatic lymphnodes, and a few anterior mediastinal nodes. Fresh lobular pneumonia of the right lower lobe. Fresh hemorrhage in the pleurae of both lungs, especially the left; also in a less degree in the mucosa of the stomach. Pseudo-melanosis of the cecum and appendix. Slight atrophy of the pancreas. Very slight atrophy of the heart. Slight splenic tumor. Chief diagnosis: Addison's disease.

Case 2. This was a married woman, 41 years of age, housewife, admitted to the hospital July 16, 1930. In 1925, five years before her admission to the hospital, her neighbors stated that she did not look well; her skin showed dark and light areas. At that time she was feeling fairly well and able to do her housework.

One year later she was treated for acute cholecystitis.

In 1927 she began to feel quite weak, had a poor appetite, was very nervous and restless, and could not sleep well. Her skin became much darker with the areas of vitiligo more prominent. She was seen by her physician at this time. Her blood pressure was 72 mm. Hg, systolic. Diagnosis of Addison's disease was made. She remained in bed for one year, after which time she was up for only short intervals. Her blood pressure remained between 66 and 72 mm. Hg, systolic, and she gradually became weaker.

One year ago she had pleurisy and was in bed five weeks; after that she would be up part of the time. Her appetite was capricious. During the six weeks before admission she was in bed continuously.

There was no pain in the abdomen, but nausea and vomiting were present.

Physical examination revealed an adult female who was fairly well nourished. The skin was diffusely pigmented and showed scattered areas of vitiligo. There was no adenopathy. The chest was clear. Heart beat was quick, regular; no murmurs. Abdomen was negative. Blood pressure 60 mm. systolic and 48 diastolic. Several small areas of pigment on the base of the tongue. No pigment in vagina, anus or rectum.

Laboratory findings: Blood glucose 116 mgm.; blood urea N. 52.4 mgm.; blood chlorides 534 mgm.; blood uric acid 4.45 mgm. Urine: normal. Blood count: mild secondary anemia.

While in the hospital her blood pressure varied between 66 systolic and 48 diastolic, and 44 systolic and 28 diastolic. She became weaker, was nauseated and had some vomiting, epigastric pain, numbness and coldness in arms and legs. Before death, which occurred three days after admission and two days after beginning treatment, pain in her legs was severe.

Autopsy Findings. Pigmentation and vitiligo of skin; extreme atrophy of both adrenals; slight generalized passive congestion; healed tuberculosis of both apices, no active process; brown atrophy of the heart; recurrent chole-

cystitis; chronic lymphadenitis of lymph nodes of hilum of liver and pancreatic group; marked lymphoid infiltration and hyperplasia of thyroid.

We believe that this patient should have received many times the amount of cortical extract that was administered to her but there was no more available.

Case 3. A woman of 56 years who had had increasing fatigue and weakness for the past six years was admitted to the hospital Nov. 19, 1930, for observation. She had been considered a case of hypothyroidism since 1921 and treated with thyroid which she stated brought about some improvement. Her blood pressure had been low during this period of observation. She also stated that brownish spots had appeared on her body during this time, but that her skin had always been dark. Three years before admission her physician had made a diagnosis of mild Addison's disease. She had lost some weight. Her blood pressure was 90 systolic and 60 diastolic. Her basal metabolism was low on several determinations—about minus 28 per cent. There was no pigmentation of the mucous membranes. She was under observation in the hospital for nine days before cortical extract was started, during which time her ability to work on the ergometer without fatigue was established. Cortical extract was given twice daily subcutaneously for eight days, not including three days when it was omitted. Her ability to do work on the ergometer without fatigue was decidedly increased, reaching twenty-eight times the control level thirteen days after the extract was discontinued. Her basal metabolism remained unchanged. After discharge from the hospital she was without treatment for fifty days, during which time her ability to work on the ergometer was two to three times greater than it had been before the institution of treatment. Thyroid, 0.12 to 0.18 gm. daily, was then given until her basal metabolism was brought to normal, when her ergometer reading was eight times the original. Cortical extract was added to the thyroid medication daily for nine days and then omitted. Four days after the cortical extract was discontinued she could do thirty-eight times more work on the ergometer than originally (figure 6). The patient stated that she felt stronger when taking the combined thyroid and cortical extract, and showed distinct clinical improvement, with moderate increase in her blood pressure. This improvement, however, did not parallel the remarkable increase in her ergometer readings.

In a potent cortical extract we possess a substance which may perhaps serve as a therapeutic test in Addison's disease and which possibly may be of value in testing and treating other forms of adrenal insufficiency. Numerous investigators have used adrenal preparations in the treatment of hyperthyroidism. Shapiro and Marine reported the beneficial effect of a glycerol extract of the adrenal cortex in a case of Graves' disease. This was administered by mouth.

A boy of 19 years with clinical hyperthyroidism, who had never received iodine, rested for three weeks in the hospital before treatment was begun. During this time his basal metabolism remained between plus 25 and plus 30

per cent on several determinations. Cortical extract was then given daily for eighteen days. During this period he became able to do twice as much work on the ergometer as he had been able to do during the initial rest period. After the extract was discontinued, this ability to work increased to three times. There was no essential change in his basal metabolic rate. In the cases of Graves' disease reported by Marine and his co-workers a drop in the basal metabolism did not occur until treatment had been going on for a much longer period. Unfortunately treatment in our case could not be continued longer.

Experiences in the relief of muscular fatigue led us to try cortin for the relief of two cases of muscular atrophy in men over fifty. In each case weakness began in the shoulder girdle. In each the muscular fibrillation disappeared during treatment. In one, an early case, the grip returned to normal in the hand affected. In the other, marked muscular cramps disappeared, to return when treatment was discon-

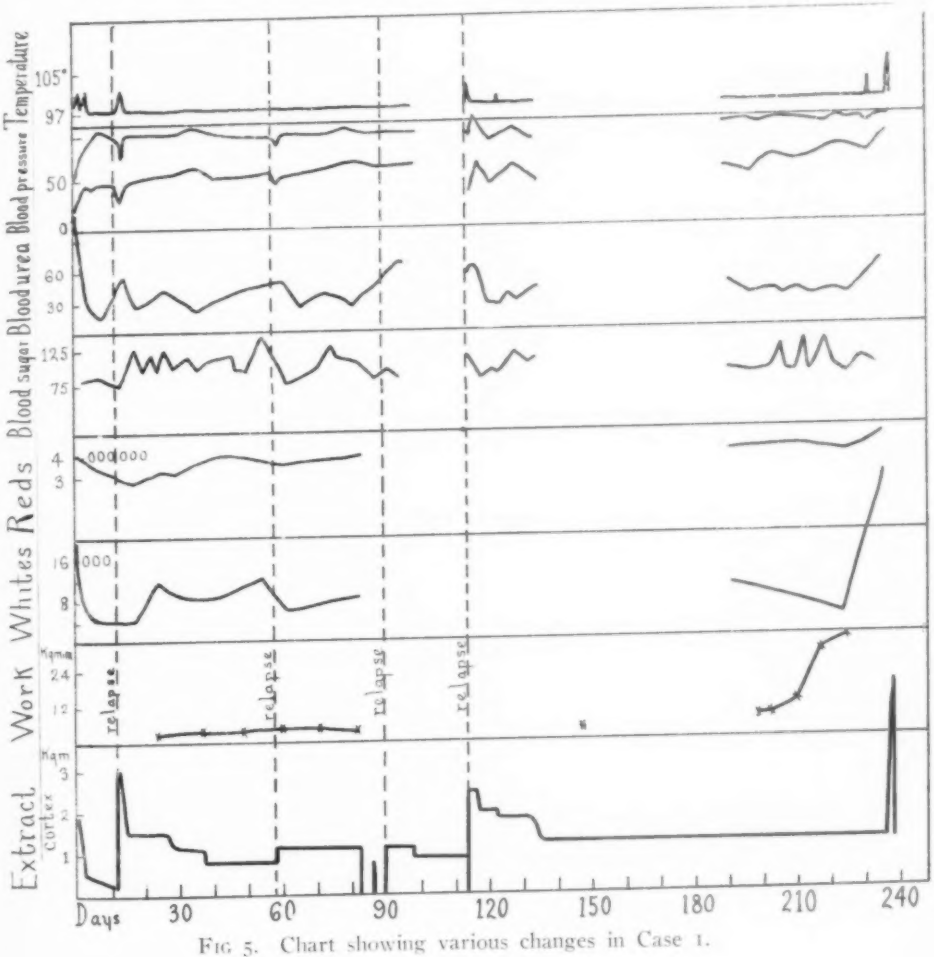

FIG. 5. Chart showing various changes in Case 1.

tinued. In a woman of 23 with the Landouzy-Déjérine type of muscular dystrophy treatment was followed by a marked increase in her capacity on the ergometer, and decidedly better rest during sleep.

A few cases of marked post-infectious asthenia have shown clinical improvement following the use of cortin, with decided increase in capacity on the ergometer.

Summary

A potent cortical extract has been administered to two cases of practically complete adrenal insufficiency.

In the first case it was of undoubted benefit. Following its use the patient recovered from a very critical state. That it kept him alive for nearly eight months was indicated by four definite relapses which followed its reduction or its discontinuance. Readministration or increase of dosage in each relapse was followed by return to his former level. He was making slow but definite improvement when bronchopneumonia caused his death.

The period of treatment in the second case was obviously too short for observation to be of any value.

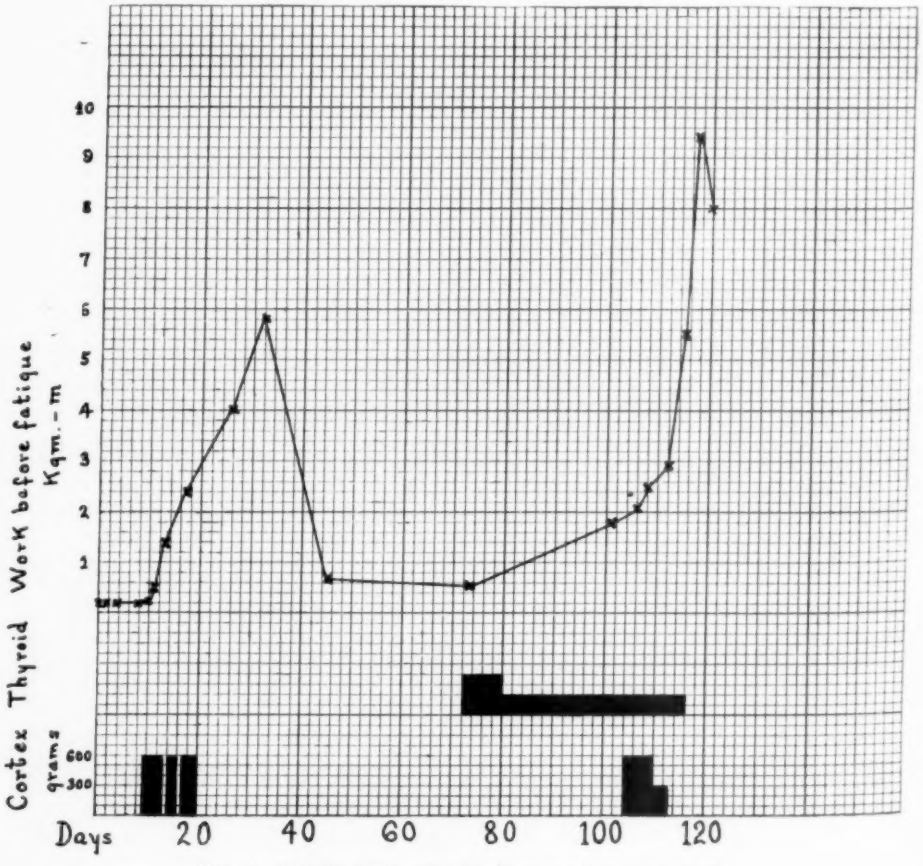

Fig. 6. Work performed by Case 3 after treatment.

A third case, one of much less severity, has shown a remarkable increase in her ability to work without fatigue. Clinical improvement has not kept pace with this increase.

One case of hyperthyroidism has exhibited decided clinical improvement following the use of the extract alone.

Two cases of muscular atrophy and one of muscular dystrophy have shown some improvement.

There is evidence that cortical extract reduces the asthenia which follows certain infections.

This study was aided by grants from the National Research Council and the Ella Sachs Plotz Foundation.

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The Relation of the Parathyroid Glands to Calcium Metabolism*†

By Harold A. Bulger, M.D., and David P. Barr, M.D., F.A.C.P.,
St. Louis, Missouri

THE profound influence of the parathyroid glands on calcium metabolism is apparent from both experimental and clinical studies. Removal of these glands results in a marked decrease in serum calcium, tetany, and in retention of calcium in the body. By means of the parathyroid extract of Collip[12] it is possible not only to relieve the tetany but also to restore approximately normal conditions of calcium metabolism. Large doses of parathormone cause, in normal animals, hypercalcemia, hypotonicity of muscles, a great increase in the excretion of calcium in the urine, a deposit of calcium in the tissues, and decalcification of bone. Furthermore Jaffe and Bodansky[23] have recently shown that the injection of parathormone may form lesions resembling fibrous cysts in bone.

These changes from overdosage with parathyroid extract occur to a variable degree in different animals. Although several species are quite resistant, the effect in man is well defined. The tetany following accidental complete parathyroidectomy can be controlled over long periods. Hypercalcemia may be produced by large doses in individuals whose parathyroid glands are presumably normal. In Hunter's[22] case of a house painter with lead poisoning, daily doses of 30 to 60 units of parathormone caused, in eleven days, a rise in serum calcium to 19.8 mg. A patient observed by Aub[1] demonstrates the source of the negative calcium balance in experimental hyperparathyroidism. This patient with otosclerosis was treated with parathormone for 42 days during which he lost 1.5 kilograms in weight, a change which would have accounted for 75 mg. of calcium if the loss of calcium had been derived from blood fluid and protoplasm. Actually he lost 17.0 grams of calcium which must have been derived from the bones.

Clinical hyperparathyroidism, presenting the identical features effected by injecting parathyroid extract, is now recognized as a definite entity. It is encountered most often in association with the multiple lesions of osteitis fibrosa cystica (von Recklinghausen's disease of bone). In addition to bone cysts, giant cell tumors and general decalcification, features which have long been considered characteristic, there have been, in many cases, a hyperplasia

*From the Department of Medicine, Washington University and Barnes Hospital, St. Louis, Mo.

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or tumor formation of the parathyroid glands, hypercalcemia, greatly increased calcium excretion in the urine, deposition of calcium in the tissues (the so-called metastatic calcification of Virchow) and occasionally the formation of stones in the urinary tract. The simulation of experimental hyperparathyroidism is so striking that there is reason to believe that the entire picture of osteitis fibrosa cystica is secondary to the increased activity of the parathyroid glands. Whether or not this be true, operation has demonstrated in a number of cases how completely the clinical condition can be arrested by removal of parathyroid tumors of hyperplastic parathyroid tissue. The effect upon the level of calcium in serum is well shown by Table 1 which includes the cases of osteitis fibrosa cystica in which parathyroid tissue has been removed for therapeutic effect.

In 16 out of 18 cases one or more tumors of the parathyroid gland were removed. The removal of the parathyroid tissue not only lowered the level of the calcium in the serum and transformed the previous negative balance into a retention of calcium but stopped the progress of the disease and arrested the formation of bone cysts and tumors. Recalcification of bone and recession of the cysts and tumors has been demonstrated. The marked drop in serum calcium indicated by the table was observed soon after operation and in many instances, although not all, returned after a few weeks to a normal level. In the case of Barrenscheen and Gold[4] a normal sized gland imbedded in the thymus was taken away without beneficial effect on the patient's symptoms and without change in the calcium level of the serum. In DuBois's[14] case, however, two normal looking parathy-

TABLE I

	Calcium Milligrams Per Cent	
	Before Operation	After Operation
Barr, Bulger and Dixon[3]	16.6	4.1
Barr and Bulger[2]	16.7	8.3
Barrenscheen and Gold[4]	14.2	16.0
Beck[5]	above normal	tetany
Boyd, Milgram and Stern[8]	17.6	5.0
Compere[13]	11.0	7.0
DuBois[14]	16.5	13.9
Eggers[16]	14.6	5.7
Gold[18]	13.1	9.6
Hunter[20]	16.7	8.0
Hunter[21]	15.0	6.7
Lanz[25]	....	....
Mandl[26]	18.2?	13.0
Olch and Bulger[28]	16.2	8.3
Pemberton and Geddie[31]	17.7	7.6
Quick and Hunisberger[32]	15.8	5.6
Snapper[35]	23.6	6.6
Wilder[38]	13.2	7.1

roid glands were removed with apparent clinical improvement.

Although osteitis fibrosa cystica may be the only condition which can be called with any probability a primary hyperparathyroidism, there are other bone diseases which may at times present comparable disturbances of calcium metabolism. Multiple myeloma is a condition accompanied by a high degree of bone destruction and it has been noted frequently in roentgenological examinations that there is a marked decalcification and rarefaction even in those portions of bone which are not actually involved in the tumor process. Metastatic calcification with deposit of calcium in lungs, gastric mucosa and kidneys has also been noted in multiple myeloma. Bulger and Barr[10] studied a patient presenting these associations, including hypercalcemia, a negative calcium balance and metastatic calcification in whom there was generalized hyperplasia of the parathyroid glands. Apparently a similar condition may also occur in metastatic tumor of bone. Klemperer[24], in 1923, reported a case in which a tumor of the parathyroid gland was found in association with carcinoma of the breast and osseous metastases. It, therefore, appears that we may have a state in which hyperparathyroidism is associated with obviously primary bone disease. The following cases are presented as examples of this clinical picture.

Case 25209: Barnes Hospital. This was a man 39 years old who had gradually increasing pain in the back for three years. Abdominal pain developed and became so severe that his gallbladder and appendix were removed in another hospital seven months before admission. Later, extreme muscle weakness became a prominent feature. Physical examination revealed marked pallor and great emaciation. There was evident mental depression and confusion. The red blood count was 1,900,000 with 35 to 40 per cent hemoglobin and a slight leucopenia. The non-protein nitrogen was 63 mgm. per cent. The x-ray of the spine showed a general loss of calcium throughout, and narrowing of the bodies of the second lumbar, and ninth and twelfth dorsal vertebrae. The bony texture was uniform and the intravertebral spaces preserved. The pelvis showed irregularly outlined areas of rarefaction, the calvarium, clean-cut skull defects with some areas of marked mottling, indicative of an invasive process of finer type. The patient's serum calcium ranged from 15.8 to 16.5 mgm. per cent. Probably because of the kidney insufficiency the serum phosphate was elevated to 6.3 mgm. per cent. The non-protein nitrogen was 63 mgm. per cent and the phenolsulphonphthalein excretion was only about 5 per cent. The urine showed a slight amount of albumin and a few granular casts. The urine also showed Bence-Jones' protein. The pathological process in the bones as revealed by x-ray was evidently malignant disease which was considered more like multiple myeloma than metastatic carcinoma. X-ray examination of the gastro-intestinal tract and pyelograms of the urinary tract were negative. This patient died at home and no autopsy was made.

Case 27621: Barnes Hospital. This patient was a moderately obese woman, 49 years old, who had been bothered with chronic constipation. For about a year she had had dull pains in the lumbar and sacral regions and later in the left lower quadrant. She had recently shown evidence of mild diabetes mellitus. About three weeks before admission she collapsed from great weakness and began to have spells of nausea and vomiting. In the hospital her chief complaint was generalized weakness although at times the pain in her back was quite severe. She showed evidence of some loss of weight. The heart was moderately enlarged, regular and a little rapid. There was slight dependent edema. The blood pressure was 170/70. The red blood count was 2,900,000 with 55

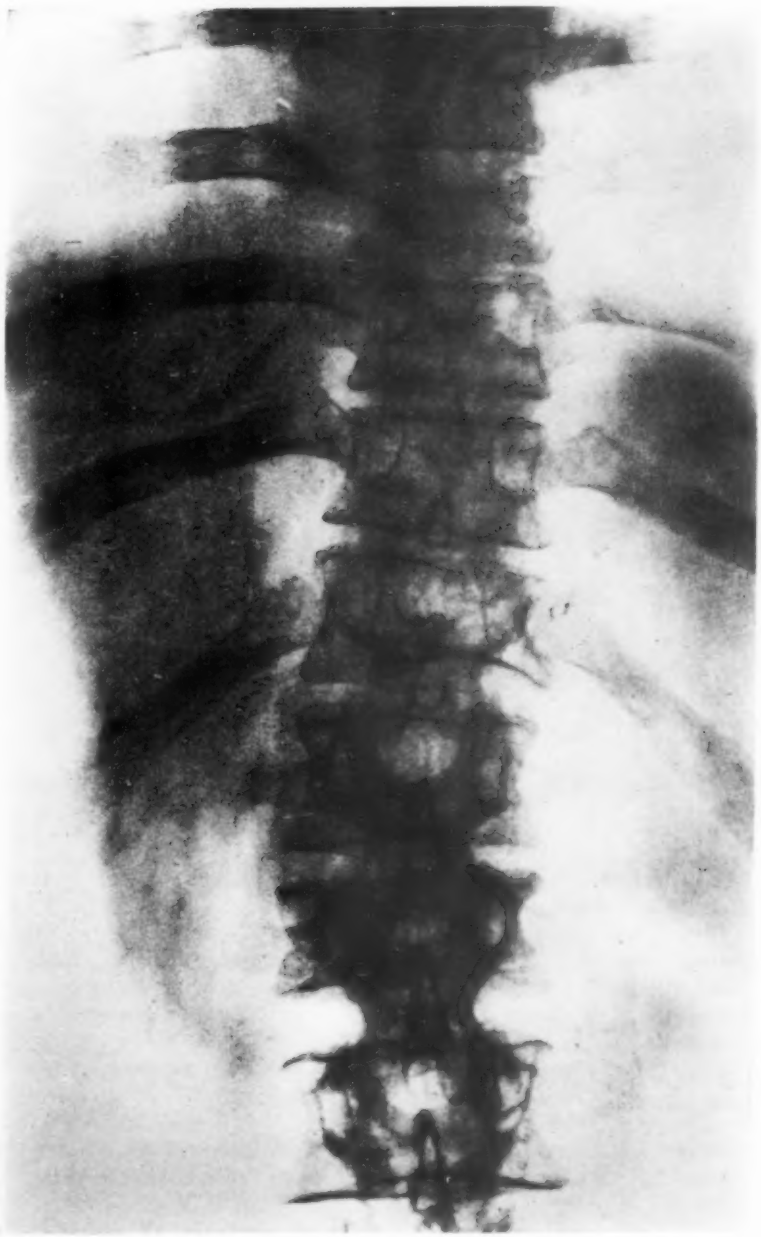

FIG. 1. Spine of Case 25209 showing general decalcification with narrowing of the bodies of the ninth and twelfth dorsal and second lumbar vertebrae.

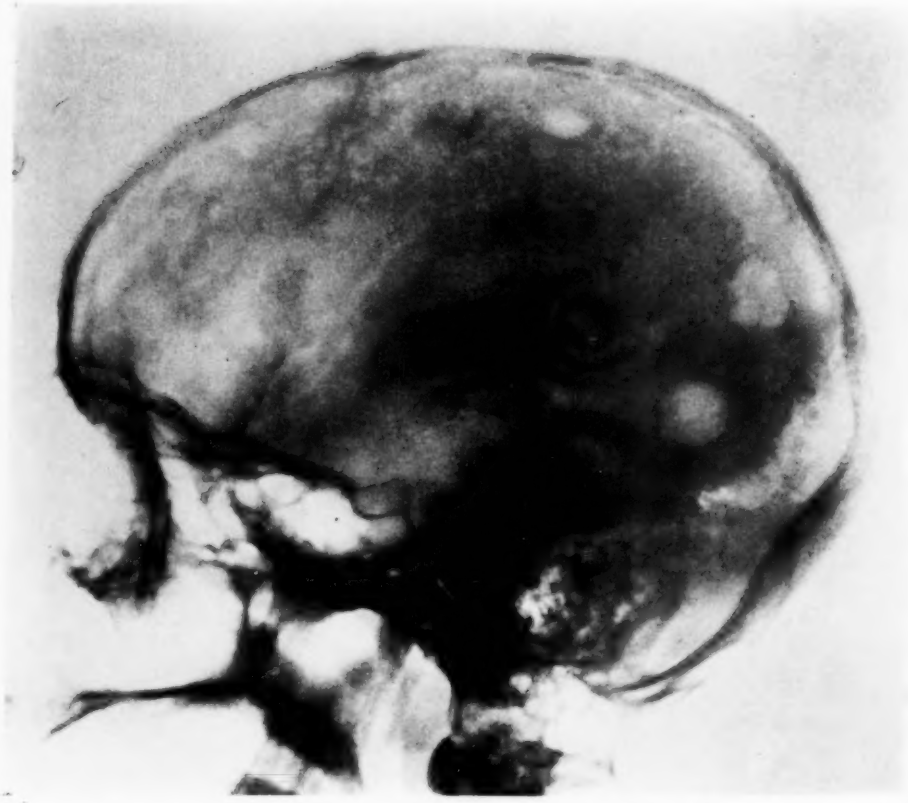

FIG. 2. Skull of Case 25209 showing clean cut bony defects with some areas of finer mottling.

per cent hemoglobin. The non-protein nitrogen varied from 50 to 67 mgm. The urine contained a slight amount of albumin and numerous white blood cells. Bence-Jones' protein was never demonstrated. X-ray examination of the spine showed a marked decrease in density throughout the bodies and there was a symmetrical collapse of the fourth dorsal vertebra. The third and sixth dorsal vertebrae also showed considerable alteration in bony texture indicating that the involvement was somewhat greater than in the other bodies (figure 3). The skull showed multiple areas of rarefaction, varying in size and character (figure 4). The bone lesions were thought most likely to be metastatic carcinoma. Careful search, including x-ray examination of the gastro-intestinal tract did not reveal anything that could be considered a primary site. This patient's serum calcium ranged between 16.5 and 18.3 mgm. per cent, phosphate between 4.0 and 4.9 mgm. per cent. Further studies showed she was on a slightly negative calcium balance. The amount of calcium excreted in the urine was greater than would have been expected with the demonstrated degree of kidney insufficiency. Since discharge from the hospital she has been failing slowly.

Case 22810: Barnes Hospital. This was a woman of 41 years of age who had suffered from a manic-depressive psychosis. For four months she had noted a pain in her right leg which was unaccompanied by any physical signs. X-rays taken at this time were considered negative except for unusual

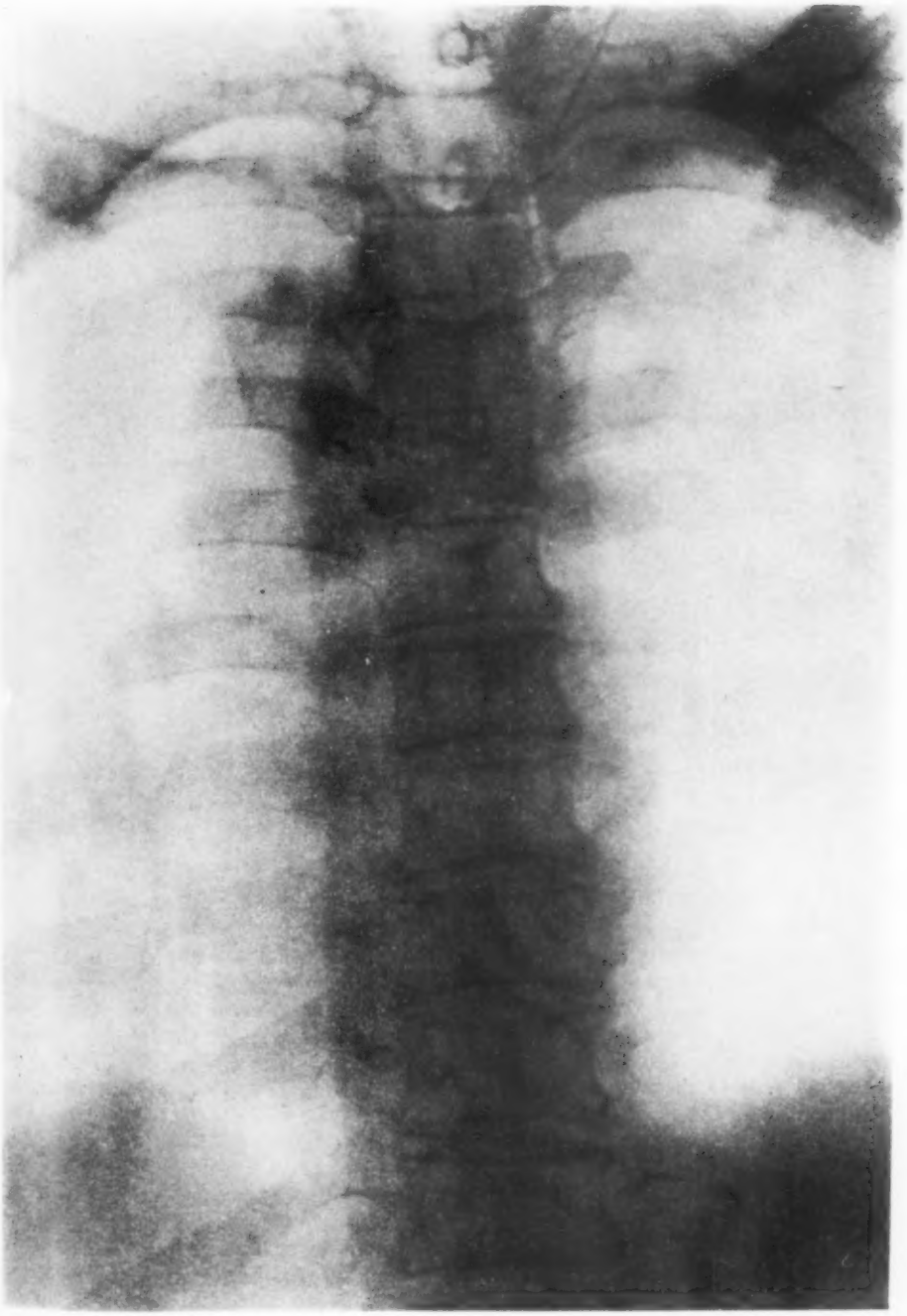

FIG. 3. Spine of Case 27621 showing general decalcification with collapse of the body of the fourth dorsal vertebra and slighter changes in third and sixth dorsal vertebrae.

FIG. 4. Calvarium of Case 27621 showing multiple areas of rarefaction.

calcification in the pelvis. Later consideration showed that the lesser trochanter of the right femur could not be seen (figure 5). In three months she was again complaining of the same pains in the right leg. X-rays then revealed that in this short interval an extraordinary degree of decalcification had occurred with rarefaction of the head and neck of each femur and with loss of bone substance in the neck of the right femur and the superior portion of the acetabulum (figure 6). Similar changes were noted in the ascending ramus of the right pubis and the first segment of the sacrum. There was a large defect in the neck of the right femur and in the upper third of the shaft. X-ray of the skull disclosed many localized areas of decalcification. She proved to have a marked hypercalcemia, the serum calcium ranging from 13.5 to 15.1 mgm. per cent, low serum phosphate varying from 2.5 to 2.6 mgm. per cent. Shortly after x-rays were taken she fractured her right femur, an injury which she survived for only five months. Autopsy revealed hypernephroma involving the adrenal, both kidneys, the femur and pelvis. The acetabulum was entirely destroyed and there was a large tumor mass extending into the pelvis from the right side and pressing on the rectum. It is most unfortunate that permission to examine the parathyroid glands was not obtained. Of particular interest in the post mortem examination were the kidneys which showed a deposit of calcium about the tubules similar to metastatic calcification and

FIG. 5. X-ray of right hip of Case 22810 taken at time of admission to the hospital and showing abnormal area of calcification in pelvis, absence of lesser trochanter, but little other evidence of decalcification or destruction.

FIG. 6. X-ray of right hip of Case 22810 taken three months after X-ray in figure 5, showing decalcification with loss of bone substance in the neck of the femur and superior portion of the acetabulum as well as destruction of a portion of the ascending ramus of the right pubis. There is also a large defect in the shaft of the femur.

quite like that previously described with osteitis fibrosa cystica and multiple myeloma.

Cases with malignant disease of bone presenting hypercalcemia are listed in Table II.

TABLE II

Condition	Author	Calcium Mgm. Per Cent
Proven cases of multiple myeloma	Carlton[11]	12.0 to 16.0
	Durman[15]	16.1
	Barr and Bulger[2]	16.0 to 17.8
	Bulger[10]	13.4
	Soper and Stroud[36]	12.6 to 16.0
Myeloma or metastatic tumor of bone	Francis Smith[34]	16.0 (approx.)
	Francis Smith[34]	16.0 (approx.)
	Belden[6]	15.3 to 18.7
	No. 25209	15.8 to 16.5
	No. 27621	16.5 to 18.3
Metastatic tumor of bone	No. 22810	13.5 to 15.1

Parathyroid hyperplasia has been demonstrated by Erdheim[17] in spontaneous rickets in animals, and by Pappenheimer and Minor[30] in rickets in children. Enlargement of the parathyroid has been recorded in osteomalacia. These findings raise the question as to the relation of the parathyroid glands to the disturbed calcium metabolism of these conditions. One finds in rickets and osteomalacia abnormalities of calcium metabolism quite distinct from those characteristic of hyperparathyroidism. In contrast to hyperparathyroidism one finds in both conditions a tendency toward a low serum calcium and tetany. Both have an increased elimination by the gastro-intestinal tract but very small amounts of calcium in the urine. Therefore, it does not appear that there is any direct relation between the abnormalities presented and an increased activity of the parathyroids. Some of the abnormalities are like those found in hypoparathyroidism but the bone pathology and negative calcium balance are distinctly different. It would seem that the hyperplasia of the parathyroid glands in rickets and osteomalacia is not a primary factor but is of the nature of a compensating mechanism. It might be noted that parathormone will relieve the tetany of both conditions and we have noted the transformation of a negative into a positive calcium balance in a case of osteomalacia on administration of parathormone.

The principal condition responsible for the development of rickets and osteomalacia is a deficiency of ultraviolet radiation and vitamin D. The relationship between these factors and the activities of the hormone of the parathyroid glands is so intimate that their functions in relation to calcium metabolism cannot well be discussed separately. The action of large amounts of vitamin D (irradiated ergosterol) is strikingly like parathyroid extract. It causes an increase in calcium in the serum, metastatic calcification and an increased excretion of calcium in the

urine. Absence of vitamin D may cause a decrease in serum calcium and tetany. Several authors have suggested that vitamin D exerts its influence by directly stimulating the parathyroid glands. Morgan and Garrison[27] have demonstrated, however, that there is actually a variation in effectiveness of parathormone depending upon the amount of vitamin D in the body. The experiments of Rosello and Petrillo[33] have indicated that after the absence of radiant energy for some time parathyroid extract is relatively inactive. Again, it has been shown that after removing the parathyroid glands, vitamin D is much less active. It appears, indeed, that the more thoroughly parathyroid tissue is removed, the less effective is vitamin D. Taylor, Branion and Kay[37] showed that when complete eradication of parathyroid tissue is assured by removing all tissue of the region including the thymus, huge doses of irradiated ergosterol were required to raise the calcium of the blood. Thus some doubt is cast upon its efficacy. It should be noted, however, that Pappenheimer[29] has demonstrated that cod liver oil and irradiated ergosterol in therapeutic doses are antirachitic in the absence of the parathyroid glands.

The clinical diagnosis of hypoparathyroidism may be indicated by the history of thyroidectomy and the occurrence of tetany. In the opposite condition of hyperparathyroidism, tumors in the region of the thyroid have occasionally been palpated but are easily confused with adenomata of the thyroid gland. Ordinarily disturbances in calcium metabolism offer the best evidence of abnormal parathyroid function and consist of changes in the level of serum calcium, in the excessive excretion of calcium in the urine, in decalcification of the skeleton and deposit of calcium in the tissues. Metastatic calcification can be discovered only at autopsy while the determination of calcium balance is much too cumbersome, difficult and time-consuming to be applied as a clinical test. The level of serum calcium remains, therefore, as the most readily ascertainable diagnostic method. It is of interest to consider to what extent disturbances in the level of serum calcium reflect changes in parathyroid function and to inquire what factors other than the parathyroids may influence calcium values.

It is important to emphasize the remarkable constancy of the serum calcium and that such an adjustment to a definite level is quite necessary because fluctuation in the concentration of calcium may cause profound changes in many physiological processes. The activity of the parathyroid glands appears to be concerned, primarily, with this regulatory mechanism. It is surprising that administering large quantities of calcium by mouth may have little or no influence on the amount of calcium in the blood. After administering calcium salts intravenously the calcium in the blood promptly returns to normal. Rapid destruction of bone may cause no rise in serum calcium. With extensive malignant disease of bone, after comminuted fractures and with bone atrophy from disuse, serum calcium may be quite normal.

Other factors may influence the level of calcium in the blood. Aside from the fluctuations of serum calcium re-

lated to vitamin D or parathyroid activity, the two factors which have a significant influence on calcium are the concentrations of serum phosphate and serum protein. The calcium will rise and fall directly with the protein although the changes due to this factor are not great. Conditions producing a high serum phosphate, however, may be attended by a considerable reduction in the calcium. This phenomenon is most commonly seen in chronic nephritis with phosphate retention. It should also be noted that low serum calcium and even tetany may be associated with chronic diarrhea.

While the estimation of serum calcium is of undoubted diagnostic importance in indicating hyperparathyroidism, it appears that there may be an increased activity of these glands with an increased excretion of calcium and a large amount of calcium in the urine without obvious rise in the serum calcium. Aub[1] notes that 50 units of parathormone may not markedly influence the serum calcium level of a normal individual, while approximately doubling the excretion. Three of the cases included in Table I had relatively normal serum calcium although they were undoubtedly examples of clinical hyperparathyroidism and responded typically following the removal of parathyroid tumors. The bone lesions similar to those of clinical hyperparathyroidism which Jaffe and Bodansky[23] have apparently produced in animals are not necessarily accompanied by any increase in the serum calcium. It appears that patients with hyperparathyroidism who develop marked kidney insufficiency may have enough phosphate retention in the blood to maintain a normal serum calcium. Bulger, Dixon and Barr[10] have described in detail their experiences in reducing calcium to normal in two patients with hyperparathyroidism by administering phosphate solutions by mouth. This undoubtedly did not change the activity of the parathyroids but produced the effect by increasing the phosphate in the blood.

Hypercalcemia was noted clinically by Hess and Lewis[19] in children who were receiving relatively large amounts of the irradiated ergosterol but it seems unlikely that this would be encountered in the average clinical experience and under the circumstances would hardly be confused with hyperparathyroidism. The occurrence of high serum calcium reported in gout and chronic arthritis has not been confirmed. High serum calcium was noted by Brown and Roth[9] in polycythemia, but Benedict and Turner[7], in a study of nine cases, did not find these high values. In three cases of polycythemia observed in this clinic the calcium was normal. It seems doubtful that any factors of clinical importance other than an increased activity of the parathyroids will cause a definite and continuous elevation of the serum calcium.

Conclusions

The influence of the parathyroid glands on calcium metabolism is apparent not only after removal of the parathyroids and the administration of parathyroid extract but also in clinical hyperparathyroidism, a condition which appears most often in association with osteitis fibrosa cystica but also with multiple myeloma and metastatic tumors of bone.

The level of serum calcium is the best index of parathyroid function and is of such diagnostic importance that its use as a test should be applied in all cases with general disease of bone and in all conditions in which there may be a disturbance of calcium metabolism. The serum calcium, however, does not always reflect either disturbances of calcium metabolism or changed activity of the parathyroid glands. It may be normal even with marked disturbances of calcium metabolism. In evident hyperparathyroidism it appears that serum calcium may occasionally be within normal limits. Low serum calcium may be due to a lack of vitamin D or to an increase of phosphate in the serum. These conditions, however, are not likely to be confused with hypoparathyroidism. Hypercalcemia usually indicates an increased activity of the parathyroid glands.

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The Etiology and Treatment of Diabetes Insipidus*†

By T. B. Futcher, M.B., F.A.C.P., *Baltimore, Md.*

THE chief purpose of this paper is to recount briefly the historical development of our knowledge concerning the etiology of diabetes insipidus up to the present time.

According to Hirsch, the earliest account of a sweet taste of the urine in certain patients comes from India and is to be found in the Ayur Veda of Sustra. Although certain symptoms of diabetes were known to the Greek, Roman and Arabian physicians, it remained for Celsus, a Roman physician, in the latter half of the second century of the Christian era to describe its outstanding symptoms. Aretaeus, of Cappodocia, a Greek physician practicing in Rome, and a contemporary of Celsus, is said to have first used the word diabetes (διαβήτης, a siphon). These early accounts deal with the saccharine type.

Thomas Willis, Sidley Professor in Oxford University, in his "Pharmaceutice Rationalis" published in 1674, was the first European to describe the sweet taste of the urine, and he is credited with having differentiated a saccharine and a non-saccharine variety, but it remained for Johann Peter Frank, in 1794, to first definitely recognize that there were two distinct forms of the disease. In one the urine possessed a honey-like taste, *diabetes mellitus,* or *verus,* in the other the urine had an insipid taste, *diabetes insipidus,* or *spurius.* Frank, first gave us a definition of diabetes insipidus, when he described it as a long-continued, abnormally increased secretion of non-saccharine urine which is not caused by a diseased condition of the kidneys. A better definition could hardly be devised for the present day.

Robert Willis, in 1838, proposed a classification of diabetes insipidus cases according to the urea excretion: *hydruria* included those cases where there was polyuria and a normal urea output; *azoturia,* those with polyuria and increased urea excretion; *anazoturia,* those with polyuria and diminished urea elimination. Subsequent experience showed that these did not represent distinct types of the disease.

From 1849, when Claude Bernard published the results of his famous piqûre experiments on the medulla of animals, the investigation of the cause of diabetes insipidus entered the experimental stage. His so-called diabetic center is situated in the floor of the fourth ventricle near the tip of the calamus scriptorius and between the centers of the pneumogastric and aud-

*From the Department of Internal Medicine, Johns Hopkins University.

†Presented at the Baltimore meeting of the American College of Physicians, March 26, 1931.

itory nerves. Puncture of this center in dogs caused a glycosuria. Puncture at a point a little lower caused a polyuria, whereas punctures at a point a trifle higher in a frontal direction, he claimed, produced an albuminuria.

Eckard, of Giessen, in 1870, confirmed Claude Bernard's findings and stated that there were other areas of the brain, injury of which in animals produced a transitory or permanent polyuria. Kahler, writing about the same time, came to similar conclusions.

In 1905, Eric Meyer advanced the view that diabetes insipidus was due to the inability of the kidneys to concentrate urine. In order to dilute the serum of the blood so that the contained sodium chloride and nitrogenous products could be excreted by the kidneys, the patient was forced to drink more water, which led secondarily to an increased output of urine. This theory received some support but was soon abandoned, for it was shown later by various investigators that the kidneys of patients with this disease were capable of eliminating a concentrated urine, that is, a urine with a specific gravity approaching the normal.

Since 1910, there has been a very active investigation of the cause of diabetes insipidus. The following three views, in succession, have been advanced:

(1) That it is caused by disturbed function of the posterior lobe of the hypophysis.

(2) That it is produced by organic changes involving one or more of the structures comprising the hypothalamus, and

(3) That there is a center, the *nucleus supraopticus* or *nucleus paraventricularis* located in the hypothalamus near the floor of the third ventricle, that presides over normal water metabolism; that nerve fibres originate in this center and pass down through the hypothalamus and infundibular stalk and spread throughout the entire posterior lobe and even between the cells of the pars intermedia; and that a lesion involving any part of this tract, the *tractus supraoptico-hypophyseus*, may so disturb water regulation that diabetes insipidus results.

The Hypophysis Conception

A brief review of the functions of the various parts of the hypophysis is important in a consideration of its possible relationship to the etiology of diabetes insipidus. It consists essentially of the anterior lobe, the posterior lobe or pars nervosa, and the pars intermedia, an epithelial envelope which partially surrounds the posterior lobe.

The anterior lobe is a glandular structure, of ectodermic origin, and derived from Rathke's pouch. Its two chief functions are concerned with growth and the development of sex characteristics. We are not concerned with the activity of the anterior lobe in this discussion.

The true function of the pars intermedia still remains a debatable question.

The posterior lobe is of nervous origin, and, until recently, has been thought to consist essentially of neuroglia cells and fibers. The recent work concerning the histology of this lobe will be deferred for a later discussion. At its upper portion it is connected with the mid-brain, or hypothalamus, by the infundibular stalk.

The chief actions attributable to the extract of the posterior lobe of the hypophysis are its pressor, diuretic-antidiuretic, oxytocic, and melanophore-expanding properties. Whether these actions are due to a single substance or to one or more different products still remains a disputed question. Abel and his associates claim to have produced all these actions from the pituitary tartrate they have isolated from the posterior lobe. On the other hand, Kamm, Grote, Rowe and Bugbee have isolated two factors, vasopressin, which exerts the pressor effect, and oxytocin, which causes contraction of smooth muscle. Gargle, Gilligan and Blumgart have shown that the antidiuretic effect is linked up with the vasopressin factor.

For several years following 1910, the theory that diabetes insipidus was dependent upon lesions of the hypophysis held sway. Only a brief reference to some of the evidence supporting this conception can be given. In 1910 Harvey Cushing, in reporting the results on the removal of the posterior lobe in dogs, found that this operation was often followed by a transitory polyuria.

In 1913 Cushing, in his Shattuck lecture, stated that in his first 100 cases of pituitary disease polyuria had been so marked in six cases that it had led to a diagnosis of diabetes insipidus by the physicians referring the patients.

The first clinical report showing a relationship between diabetes insipidus and lesions of the hypophysis was made in 1912 by E. Frank. He reported a case in a man who had been shot and x-rays revealed the fact that the bullet was lodged in the sella turcica.

In the following year, 1913, M. Simmonds reported a case of diabetes insipidus in a woman, aged thirty-seven. Two months after an excision of the breast for carcinoma she developed a marked polyuria and polydipsia. The autopsy showed, in addition to numerous other metastases, one involving and destroying the posterior lobe of the hypophysis. The metastasis pressed on the pars intermedia but did not involve it or the anterior lobe.

Following these two reports numerous similar cases soon began to appear in the literature, apparently confirming this relationship.

An additional support was given to the posterior lobe conception by the appearance of reports in 1913 by von den Velden and Farini, working independently, that the hypodermic injection of pituitrin had a marked effect in reducing the polyuria and polydipsia in this disease.

As a result of the above evidence, it was natural that the view that diabetes insipidus was due to disturbed function of the posterior hypophysial lobe should have gained rather general acceptance.

The Hypothalamic Conception

While the hypophysial idea of the cause of diabetes insipidus was gaining ground, some experimental work appeared casting doubt on it, and indicating that the lesion was not in the posterior lobe but in the hypothalamus.

The hypothalamus, or mid-brain, forms the floor of the third ventricle. It consists essentially, from before backwards, of the optic chiasm, the tuber cinereum, and corpora mamillaria. In addition there is the infundib-

ulum, situated below the tuber cinereum and terminating in the infundibular stalk, which is attached to the upper surface of the posterior lobe of the hypophysis.

The question of the relationship between polyuria and experimental lesions of the hypothalamus in dogs was first undertaken by Camus and Roussy in 1913. They reported that they had been able to produce transitory polyuria by puncturing the hypothalamus of dogs through the sphenoidal bone with a heated drill. In one dog a permanent polyuria, as well as a dystrophia adiposogenitalis, resulted. They believed that it was injury to the tuber cinereum that produced the polyuria.

These investigators continued their experiments, and in 1920 reported what seemed rather convincing evidence that the polyuria does not depend on a lesion of the posterior hypophysial lobe, by producing it in a dog from which the hypophysis had been previously removed. The investigations of Aschner, and of Houssay and Hug supported the findings of Camus and Roussy.

Bailey and Bremer, in 1921, reported from Cushing's Clinic a very careful piece of experimental work on dogs confirming the views of Camus and Roussy. With the technique used by the latter there was always risk of injury to the pituitary. By a special surgical technique Bailey and Bremer exposed the hypothalamus by the temporal route, which permitted an exposure of the whole region. The punctures of the hypothalamus could be made where desired, and the pituitary, being in plain view, could be carefully avoided. When the animals died or were sacrificed sections were made of the injured hypothalamus, and of the pituitary to make sure that the latter had not been damaged in the operation. In all of their thirteen dogs in which the hypothalamic puncture was performed there developed a polyuria which appeared in the first two days. According to the extent of the lesion it varied from a transient one, lasting from six to eight days, to an apparently permanent polyuria. It is interesting to note that in some of the dogs the physical effect of the puncture on the animals resembled that following hypophysectomy. Lesions of the tuber cinereum produced in two dogs a cachexia hypophyseopriva with acute genital atrophy, and in two other dogs an insidiously developing adiposogenital dystrophy. The integrity of the pituitary was in each of these cases verified histologically. It is important to note that these researches confirmed the observations of Camus and Roussy to the effect that injury to the hypothalamus, in addition to causing polyuria, also, in some instances, resulted in the production of an adiposogenital syndrome, which has been supposed to be dependent on pituitary disturbance.

Camus and Roussy, as already stated, believed that the polyuria in experimental cases was dependent upon damage to the tuber cinereum. Richter has shown that in the rat a marked and permanent increase in water-intake and urine-output can be produced by a fine puncture made in the brain stem near the hypophysis. On the other hand, Helen Bourquin produced polyuria in dogs by injuries to the corpora mamillaria.

From the clinical standpoint there was evidence that diabetes insipidus in man could be produced by hypothalamic lesions. Erdheim, of Vienna, in a publication appearing in 1904, appears to have been the first to suggest, as a result of clinical and pathological studies, that the polyurias associated with organic brain disease were actually dependent upon tumors or other lesions involving the hypothalamus. Another frequently quoted case is that of Lhermitte, published in 1922, in which diabetes insipidus developed in a case in which a syphilitic lesion involved both the tuber cinereum and infundibulum. Babonniex and Lhermitte, in 1925, reported another case of diabetes insipidus with syphilitic basilar meningitis, with lesions also involving the infundibulum and tuber cinereum. Verron reported a case following trauma, in which there was a circumscribed necrosis of the infundibulum.

In 1928 Elmer, Kedzierski and Scheps reported a case of diabetes insipidus in a patient with hypernephroma of the kidney with a metastasis in the hypothalamus. An embolus of hypernephroma cells had blocked an artery causing a necrosis of the tuber cinereum. The writer, in 1929, published the records of a case of diabetes insipidus in a man who had a primary carcinoma of the lung, with a metastasis about 1.5 cm. in diameter involving the infundibulum and tuber cinereum, with an intact pituitary.

With these reported cases there seemed very conclusive evidence that diabetes insipidus could be produced clinically and experimentally by lesions involving the structures comprising the hypothalamus without any involvement of the posterior hypophysial lobe. The suspicion began to arise that when the clinical picture of diabetes insipidus occurred in growths involving the posterior lobe, as well as in the case of hypophysial duct cysts, the cause of the polyuria and polydipsia was actually involvement of or pressure on the structures comprising the hypothalamus. In a similar way might be explained the intense thirst and polyuria that not infrequently follow the attempted surgical removal of basilar tumors in the region of the hypophysis.

The Tractus Supraoptico-Hypophyseus Conception

From the foregoing it will be seen that we have the hypophysis and the hypothalamus proponents of the cause of diabetes insipidus. In recent years the adherents of the hypothalamus conception have been getting rather the better of the argument. It now remains to present the evidence which tends to show that the adherents of both groups are right in their interpretation.

To clarify this point it is necessary to summarize the very important work that was published by Greving[1] and Pines[2] in 1926 concerning the histology of the posterior lobe of the hypophysis and of the hypothalamic region.

The posterior lobe of the hypophysis, embryologically, is of nervous origin and has until recently been supposed to be made up practically entirely of glia fibres and cells. The general impression has been that it contained no evidences of secretory cells, similar to those of the anterior lobe, which is a typical secretory gland. However, in 1927, Lewis and Lee[5] showed that it actually contained groups of cells pro-

jecting inwards from the capsule, which sometimes have a tubulo-racemose arrangement in infants up to four years.

The general belief has been that the posterior lobe contained no true nerve fibres or nerve cells. However, as far back as 1904, Berkley[3] described and pictured nerve cells with one or more processes coming off from them. Dandy[4], in 1913, reported on the external nerve supply of the pituitary. He found that it is derived from the carotid plexus of the sympathetic nervous system. These nerves follow the arteries supplying the various portions of the hypophysis, and he noted that very few went to the posterior lobe. No sections of the hypophysis itself were made to demonstrate whether or not nerve fibres could be demonstrated within the gland. Cajal, in 1911, was the first to demonstrate actual nerve fibres in the posterior lobe by his silver-reduction staining method. Nerve fibres in this lobe were later reported from Cushing's laboratory.

Greving[1] of Erlangen, and Pines[2] of Bechterew's laboratory in Leningrad, in studying the cause of diabetes insipidus, attacked the problem from the standpoint of determining whether there were any demonstrable nerve paths originating at any particular point in the hypothalamic region and communicating with the posterior lobe. Working apparently independently, they have made a contribution to this problem which appears to be of the very greatest importance. They made serial sections in an obliquely horizontal direction through the hypothalamus, hypophysial stalk and posterior lobe and stained the sections by the silver method. Their results briefly are as follows: They find that at the nucleus supraopticus and nucleus paraventricularis, situated on each side of the median line near the floor of the third ventricle and adjacent to the optic chiasm, nerve fibres arise forming a definite bundle which passes down on each side near the tuber cinereum through the infundibulum and infundibular stalk into the posterior lobe, where they form an extensive network, and surround groups of cells which are thought to form the secretion of the pituitary lobe. Some of these fibres can also be traced between the cells of the pars intermedia. Greving calls this tract of nerve fibres beginning in the nucleus supraopticus and terminating in the posterior lobe the *tractus supraoptico-hypophyseus*. The belief is that the tract belongs to the vegetative nervous system. The tentative conception is that the nucleus supraopticus is the center that presides over the normal regulation of water balance. The fact that this center is connected by a definite bundle of fibres with the posterior lobe, the extract of which has such a potent effect in relieving the polyuria of many cases of diabetes insipidus, seems to be of the greatest significance. Cushing, in his Lister lecture of 1930, emphasizes the importance of the work of Greving and Pines, and seems to accept the view that there is a water regulatory center, the nucleus supraopticus. In referring to the work of these investigators he says, "When successfully stained, however, nonmyelinated nerve fibres in abundance at first can be traced from both the supraoptic and paraventricular nuclei (though more particularly from the

former) to converge at the infundibulum, whence in a compact bundle they pass down the pituitary stalk to enter the posterior lobe. Arrived there, they not only ramify widely throughout the pars nervosa weaving themselves as Greving states, in 'basket-like' fashion around what appear to be secretory islands, but they also, according to Pines, can be traced in among the epithelial cells of the pars intermedia."

The existence of this tractus supraoptico-hypophyseus, as described particularly by Greving, renders it probable that diabetes insipidus may result from lesions anywhere along its course, as suggested by Zadek[7]. What relation this tract has with the cause of dystrophia-adiposogenitalis has not been definitely settled. Greving suggests strongly such an association. Clinically, we not infrequently find a combination of diabetes insipidus and adiposogenital dystrophy. In the polyuria produced experimentally in animals, both Camus and Roussy, and Bailey and Bremer reported that in some instances the animals manifested both diabetes insipidus and also dystrophia adiposogenitalis. It is probable that the tractus supraoptico-hypophyseus was severed in these experiments. That a disturbance in the continuity of this tract may produce both conditions was reported by Cushing in his Cameron Lectures in 1925. He and Maddox, by placing a silver clip on the hypophysial stalk of dogs, after shrinking the brain by Weed's method so as to prevent damage to the mid-brain and hypophysis, produced both polyuria and dystrophia-adiposogenitalis in the animal.

The discovery of the tractus supraoptico-hypophyseus goes a long way towards reconciling the conflicting views of the pituitary and hypothalamic adherents. We can conjecture that it may be found that tumors or other lesions involving the nucleus supraopticus, the posterior lobe of the hypophysis, or of the tract anywhere between these points may produce diabetes insipidus.

Treatment

Only a brief reference to the treatment of diabetes insipidus can be made. If the patient has a positive Wassermann antiluetic treatment should be instituted, as the polyuria might be dependent upon a gumma of the mid-brain or upon a basilar syphilitic meningitis.

Surgical interference is often indicated where there are neighborhood pressure symptoms, such as headaches, ocular palsies, bitemporal hemianopsia, and choked discs. An early operation may prevent total blindness, even though it may not materially influence the polyuria.

The hypodermic use of 0.5 to 1 cc. of surgical pituitrin often relieves the distressing thirst and polyuria. The dosage and interval between doses has to be worked out in each individual case. Usually the effect of an individual dose does not last longer than from four to six hours. Following basilar tumor operations, a distressing diabetes insipidus may develop when it did not previously exist. Frequently this polyuria and polydipsia will spontaneously disappear. If it does not, pituitrin therapy is indicated. The cause of the diabetes insipidus in these cases is probably due to damage to the supraoptico-hypophyseus tract during the operation.

Blumgart has found that the nasal administration of pituitrin is sometimes effective. A tampon of cotton soaked with pituitrin may be inserted into one nostril, or 1 cc. of pituitrin may be diluted with 30 cc. of normal salt solution and frequently sprayed into the nostrils.

In some instances it is found that pituitrin has little or no effect. Elmer, Kedzierski and Scheps[8] have proposed a classification of diabetes insipidus from an etiological and therapeutic standpoint. It is as follows:

(a) Cases due to destruction of the posterior lobe of the hypophysis. Here the posterior lobe extract fails entirely or only in part to sensitize the regulating centers for water and salt in the hypothalamus. In these cases pituitrin has a definite, though transitory therapeutic effect, because the regulatory centers in the hypothalamus are intact.

(b) Cases due to destruction of the water and salt-regulatory centers in the hypothalamus. In these the secretion of the posterior lobe is still produced, but it cannot sensitize the hypothalamic centers because they are destroyed. In this group the pituitrin has no effect whatever, since the regulatory centers in the hypothalamus are destroyed and are incapable of sensitization.

(c) Cases in which there is an interruption of the communicating nerve fibres connecting the hypothalamus (tuber cinereum) and the posterior lobe of the hypophysis. This group, they state, is insufficiently understood and requires further investigation. The therapeutic effect of pituitrin is not stated.

If the views of these authors be correct, the failure of pituitrin to act therapeutically may be referred to those cases where the so-called center or centers are destroyed.

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The Level of Oxygen Exchange in Obesity As a Factor In Planning Treatment*†

By Frank A. Evans, M.D., F.A.C.P., *Pittsburgh, Pa.*

IT IS justifiable to consider the excess weight in obesity as inactive storage tissue. We may think of the obese patient as seen, as made up of his ideal weight plus burdensome, useless fat[1, 2, 3]. Removal of the excess weight can be accomplished only by burning this fat. This is done by measures which bring about a difference between energy intake and energy output, but which do not throw on the organism unphysiological burdens. Marked lowering of the energy intake can be accomplished safely by radical limitation of diets along physiological principles. Increase of energy output by thyroid medication adds to the physiological strain to which the obese patient is subject and is, therefore, contraindicated in most cases.

Properly Limited Diets Are Safe

Marked diminution of energy intake by radical limitation of diet without physiological strain is accomplished by adjusting the food intake to the active living tissue, represented by the *ideal* weight, instead of the actual weight. Adequate protein must be given and acidosis must be kept in mind. All these factors are met by allowing one gram of protein and twenty-five calories per kilogram of ideal weight, calculating the amount of carbohydrate and fat to give a ketogenic-antiketogenic ratio of 1½ to 1, and making up the menu including this protein and carbohydrate ration and omitting the fat. By this method diets affording only four hundred to six hundred calories are obtained on which patients may be kept for months with rapid weight loss and nothing but improvement in their general condition[4]. If the observed daily weight loss corrected for water balance and nitrogen loss or gain, is considered fatty tissue and this is converted into terms of fat calories burned, these patients are seen to operate on theoretical ketogenic-antiketogenic ratios of 3+ to 1. Frequently they show an initial ketonuria and at infrequent intervals during the course of dieting, but in none has there been any evidence of acidosis. Similarly, when the carbohydrate is reduced much further and patients are fed little more than one gram of protein per kilogram of their ideal weight, acidosis does not result. When this is done, however, an appreciable negative nitrogen balance results, probably because of a diversion of some of the protein ration for its anti-

*From the Western Pennsylvania Hospital, Pittsburgh, Pa.

†Presented at the Baltimore meeting of the American College of Physicians, March 26, 1931.

ketogenic properties[5]. It has been found wise, therefore, to include some carbohydrate, not necessarily to avoid acidosis, but to function as protein-sparing food and prevent nitrogen loss. The amount determined as sufficient by observing patients in metabolic balance over long periods is three-fifths of a gram of carbohydrate for every gram of protein. The diet thus arrived at and found to be satisfactory consists then of one gram of protein per kilogram of *ideal* weight and three-fifths as many grams of carbohydrate, with no fat other than that necessary in giving the protein ration. The fat can be as low as nine grams and need never be as high as thirty grams.

With diets thus determined, 187 patients dieted for an average of 8.7 weeks lost an average of 30.5 pounds, approximately 3.5 pounds a week for 9 weeks. A variety of obscure symptoms and minor ailments disappeared, very few patients complained of hunger and all mentioned an increase in resistance to fatigue and feeling of well-being. No endocrine product was given to any of these patients. Thyroid gland administration in the treatment of simple obesity is unnecessary for satisfactory results if diets based on physiological principles are used.

Thyroid Medication Is Contraindicated

The basal metabolic rate of the obese, which is a relative measure of energy output, is normal [6,7]. If the calories per hour oxygen exchange to give this normal rate with the increased surface area of the obese is related to the ideal weight, a figure is obtained which is seen to be high. For example, a woman age 50, whose ideal weight was 131 pounds, actually weighed 206 pounds. Her calorie per hour oxygen exchange was 69, giving a basal metabolic rate when calculated in the ordinary way of plus 4, a normal figure. When related to her ideal weight, these calories per hour give a basal metabolic rate of plus 25. To have a normal basal metabolic rate for her ideal weight the oxygen exchange should have been 55 calories per hour. In other words, this patient as far as her real self, her living, useful tissue was concerned, was operating at a level of oxygen exchange associated under ordinary circumstances with thyrotoxic symptoms. This is another index of the increased burden thrown on the circulatory and respiratory system by the added weight. If a woman who weighed 131 pounds, the ideal weight of the patient mentioned, and had the same caloric exchange giving a basal metabolic rate of plus 25, were forced to carry with every move a dead weight of seventy-five pounds, represented by her excess weight, one would expect early deterioration. An increase by artificial measures of this energy output, already high because of the excess work of the obese in merely living, is unphysiological. Thyroid is, therefore, contraindicated.

Practically all the patients treated by diet alone lost more rapidly during the first four weeks than later. The 133 patients for whom weighings are available at this period lost an average of sixteen pounds. During this period they regularly reported a gratifying feeling of well-being and increased resistance to fatigue, more than could be accounted for by the mechanical relief from

the burden represented by the weight loss. With very few exceptions, also, hunger disappeared within several days. When they found they could lose thus rapidly without hunger and with a feeling of increased energy, instead of lassitude, they were encouraged to continue and this contributed to the ultimate success obtained in these patients. The probable reason for these fortunate symptoms presents another contraindication to the use of thyroid in the treatment of obesity.

Patients on this dietary régime showed a more rapid reduction in the calories per hour oxygen exchange than in weight[7]. The calories per hour of the patient presented above fell from 69 to 53, converting the basal metabolic rate calculated on her ideal weight from plus 25 at the beginning to minus 3 at the end of the dietary period. This is sufficient explanation for the increased resistance to fatigue and feeling of well-being these patients reported.

DuBois[8], and Strang and McCluggage[9] have shown that the rise in calories in response to a fixed meal—the specific dynamic action of the meal—is quantitatively the same in the obese and those of ideal weight if they are otherwise normal. Strang and McCluggage[9] also presented evidence that the feeling of satiation after food comes from the attainment of the optimum *rate* of change of metabolism in response to it. With a fixed specific dynamic action this rate of change of metabolism is of course less in relation to a high basal metabolism than to a low one. In other words, it takes more food to give a feeling of satiation in a person with a high basal metabolic rate than in one with a lower one; or conversely, the satiation from a fixed amount of food is greater with a low basal metabolic rate than with a higher. These observations related to the lowering of the basal rate of oxygen exchange observed in these patients probably accounts in part at least for their feeling of contentment with the food given.

If the drop of basal calories per hour oxygen exchange in these patients were prevented by thyroid medication, two worthwhile results now obtained probably would not occur. They would not have the increased resistance to fatigue and their appetites would not be as satisfied with the food given. They would, therefore, not feel so encouraged to continue and the ultimate results would probably not be as good.

Thyroid Medication Indicated

While the 187 patients so far discussed were being successfully treated as described, four patients were found to whom thyroid administration was thought desirable because of a slow rate of weight loss. One woman who weighed 259 pounds was first seen after three months in bed because of another disability. Her calories per hour were 59, giving a basal metabolic rate of minus 26 for her actual weight and minus 8 for her ideal weight. After four weeks of dieting the calories per hour were 54, giving a basal rate for her actual weight of minus 34 and minus 18 for her ideal weight. The other three were young women in whom initial basal metabolic rates within normal limits early in the dieting period fell to levels somewhat

below that normal for their ideal weight. They all reacted well under thyroid therapy combined with the diet, but so controlled that caloric exchanges never higher than normal for their ideal weights were obtained. No doubt each one of these patients had hypothyroid tendencies, but if they did there was no demonstrable clinical evidence of it. This observation is important in showing that there is no clinical evidence other than the basal metabolic rate by which the very rare patient in whom thyroid medication may be used to advantage can be picked out from the large group in which it is contraindicated. In these its use should be controlled by frequent basal metabolic rate determinations because if pushed to high levels the same undesired results as those discussed above for the patients in whom its use is contraindicated would, no doubt, ensue.

Conclusions:

I. Thyroid administration in the treatment of most cases of obesity is not necessary because:

1. A diet consisting of one gram of protein and three-fifths of a gram of carbohydrate per kilogram of ideal weight, and no more than fifteen to twenty grams of fat, gives diets of from four hundred to six hundred calories on which these patients come down rapidly without thyroid.

2. They may be maintained on these diets for months if necessary with nothing but improvement in their general condition.

II. Thyroid administration in the treatment of most cases of obesity is contraindicated because:

1. The calories per hour oxygen exchange giving a normal basal metabolic rate when calculated on the actual weight, if related to the ideal weight, give a figure considerably higher than normal. This represents one of the physiological strains of obesity which should not be increased by thyroid therapy.

2. The drop in the basal metabolic rates with the institution of limited diets probably accounts for the feeling of well-being and increased resistance to fatigue observed by these patients and in part for the feeling of satiation with the lowered food intake which affords contentment with the diet prescribed. This encourages these patients to persist and should not be eliminated by thyroid medication.

III. A few patients—perhaps no more than two per cent of all—do not lose weight rapidly without thyroid medication. These cannot be differentiated from the others by history or physical findings. They may be recognized with assurance only by repeated basal metabolic determinations during the course of dieting.

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The Many Sided Question of Protein In Nephritis*†

By W. S. McCann, M. D., F.A.C.P., *Rochester, N. Y.*

IN THE practical management of patients with nephritis, regardless of the type, the question of the protein metabolism assumes a position of great importance. When one considers the varied rôles played by proteins in the body, the problem of controlling or modifying their behavior becomes one of great complexity. The catabolism of protein, giving rise to urea, sulphuric and phosphoric acids, must be limited to the capacities of damaged kidneys to excrete these substances. The anabolic demands for protein must not be overlooked, as physicians have been prone to do, because new protein synthesis is often urgently needed to replace that destroyed by "wear and tear" or lost during albuminuria, and to regenerate dwindling serum proteins which have come to play such an important part in the maintenance of the water balance of the body. So prevalent has been the idea that protein catabolism exerts deleterious effects upon the kidneys and vascular system that patients are seen not infrequently with "hunger edema" due to protein starvation resulting from the severe and prolonged restriction of the protein of the diet, and states of less marked malnutrition from this cause are common. Physicians fall into the error of assuming that the sole means of reducing the catabolism of protein is that of reducing its intake, forgetting that the endogenous metabolism may remain high even though little protein is taken in the diet. It is important, therefore, that attention be called to other methods for reducing the catabolism of protein and of increasing its deposition in the body for the replacement of body proteins destroyed by the "wear and tear" of living in health or in disease, as well as protein lost during albuminuria.

The catabolism of protein in the nephritic patient is influenced by the same factors which operate in most other individuals. There is the so-called "wear and tear quota", which is heightened by "toxic destruction" in the presence of fevers of infectious origin such as those which frequently precede or accompany hemorrhagic nephritis. Furthermore, when the supplies of fat and carbohydrate are inadequate protein catabolism is increased, so that we say that fats and carbohydrates spare protein. Finally, we have to consider what happens when a man consumes more protein than is

*From the Department of Medicine, School of Medicine and Dentistry of the University of Rochester and the Medical Clinic of the Strong Memorial Hospital and Rochester Municipal Hospital, Rochester, New York.

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required to cover the irreducible minimum of wear and tear on body proteins.

A normal man, provided he were physically capable of ingesting an amount of protein sufficient to cover his energy requirement for rest in bed, would experience an acceleration of his total metabolism as the result of such ingestion so that 40 per cent more heat would be produced in his body than the food protein could furnish. The energy for this extra heat would be derived from his stores of carbohydrate and fat. Rubner and Lusk[1] have called this the "specific dynamic action" of protein. A normal man, fully grown, will quickly adjust the level of protein destruction to protein intake, so that he is in nitrogen balance, provided the total energy of the food is adequate. If he does what Sivén[2] did, namely, reduces his protein intake to lower and lower levels, his urinary nitrogen excretion will fall to a minimal level of 3 to 4 gm. per diem at which nitrogen balance can be established. In order to do this he must consume proteins of high "biological quality" in the sense of Thomas[3], that is, proteins which contain all the necessary amino-acids required for the synthesis of human body proteins. Larger amounts are required if the proteins consumed are deficient in this respect, as many of the vegetable proteins are.

If our previously normal man were to acquire typhoid fever or a streptococcal infection, nitrogen balance could no longer be established at a low level, or, in fact, at a high level, unless the total caloric intake were raised to many times the resting energy requirement as the work of Shaffer and Coleman has shown[4]. The difference between these two levels at which nitrogen balance could be established is the measure of the "toxic destruction of protein". Even in tuberculosis, which causes only a slight toxic destruction, the writer[5] found that the minimal level of nitrogen balance could be reached only when the patients were able to take from two to two and one half times the number of calories required by the patient for rest in bed.

When toxic destruction ceases and convalescence begins the wasted body seizes upon food protein with avidity and replaces that destroyed, so that nitrogen excretion may remain low even when the intake is high. The same phenomenon follows periods of partial or complete starvation. Let us apply some of these considerations to the case of a young man with acute hemorrhagic nephritis. During the attack of scarlet fever or of tonsillitis which preceded or ushered in the nephritis, toxic destruction of protein occurred and will persist as long as the infection lasts. During this period increased amounts of the end products of protein catabolism will be produced no matter how low we reduce the protein intake. As water excretion is reduced these end products are retained and usually appear in increased amounts in the blood of such patients. If we reduce the salt intake and administer water the urine volume may increase to an amount adequate to sweep the blood clear of extra urea. In such cases it is usually possible to increase the intake of carbohydrates to a high level and in this way to dimin-

ish to some extent the abnormally high endogenous metabolism of protein.

Edema will probably have occurred at first without low serum proteins. The urine will show increased amounts of serum albumin and serum globulin, fibrinogen, and hemoglobin, representing considerable losses to the body which should ultimately be replaced. The urinary globulin and the hematuria, as Van Slyke and coworkers have shown[6], give us a fair measure of the intensity of the damage to the kidney. Prolonged loss of these substances diminishes their amount in the blood, producing anemia and reducing serum proteins. Years ago Starling[7] showed that the balance between the osmotic pressure of the serum proteins and the hydrostatic pressure in the capillaries determines the escape and return of water to them. With the reduction of serum proteins the edema of our patient will tend to increase, particularly if the reduction affects chiefly the albumin fraction, which has a much greater swelling pressure than the globulin.

Experience has taught us that many cases similar to this one will undergo a transition along the following lines. The hematuria and urinary globulin will diminish greatly as the intensity of glomerular damage abates. Albuminuria and edema may increase until a clinical picture results which may closely simulate that of a primary degenerative nephritis or nephrosis, in which the predominating lesion is tubular degeneration. We have a suggestion as to how this comes about from the experiments of two of the younger workers in Christian's clinic, Barker and Kirk[8], who depleted the serum proteins of dogs by plasmapheresis and found that if this were continued tubular degeneration ensued.

Various workers have studied the regeneration of serum proteins after plasmapheresis. Kerr, Hurwitz and Whipple[9], found that the regeneration period was shortest on a meat diet, longer on bread and milk, and longest during fasting, and that it was much prolonged when the liver was injured by chloroform or excluded by Eck fistula. Epstein[10] sought to build up the serum proteins in nephrosis by giving high protein diets with considerable success. The writer, in unpublished experiments, has observed the effects of similar high protein diets on edematous patients with chronic hemorrhagic nephritis, the results of which may be summarized here. The patients invariably retained nitrogen, presumably as deposit protein, since non-protein nitrogen of the body fluids did not increase. Only a small fraction of the deposited protein appeared as circulating protein of the blood serum. The major portion of the deposit being outside the vascular system increased the water held in the tissues so that the weight increased and edema increased until the slowly increasing serum proteins reached the point at which increased diuresis and loss of edema could occur.

Before applying these results to other patients with hemorrhagic nephritis we should satisfy ourselves that the increase of protein in the ration will have no deleterious effects, produced by disturbing the mechanism for acid-base balance or by possible renal damage by protein which the work of Newburgh[13] and others suggest.

For the maintenance of the acid-base balance the kidneys play a most important part. The non-volatile sulphuric and phosphoric acids resulting from protein catabolism are excreted largely by the kidneys, though partly through the bowel. When these acids pass through the kidneys normally *ammonia is formed by the kidneys* to accompany them, as shown by the work of Nash and Benedict[11]. This normal ammonia formation prevents the loss of fixed bases and protects the alkaline reserve of the blood. In nephritis the mechanism fails in two ways. Retention of these non-volatile acids reduces the CO_2 combining power of the alkaline reserve. The ammonia forming function is frequently impaired in hemorrhagic nephritis. Observations made by Palmer and Henderson[12] in 1915 show clearly the reduced urinary ammonia of patients with renal acidosis. The failure of this function results in a drain upon the reserves of fixed bases which must accompany acids excreted in the urine, in the absence of adequate ammonia formation.

In the presence of renal damage sufficient to limit acid excretion or ammonia formation, an increase of protein in the diet is justifiable only when the catabolic processes can be limited and the anabolic augmented. Protein deposited makes no demand on the excretory mechanism or on the regulation of acid-base balance. Protein destroyed does make a great demand, but within limits this may be compensated for by increasing the basic constituents of the diet derived from fruits and vegetables or administered as the alkali-salts of citric or other organic acids. The problem of renal acidosis presents a difficulty which is not insuperable.

Newburgh[13] has raised an important question as to the possibilities of producing renal injury by protein in the diet. He was able to produce renal lesions in white rats, by feeding them diets consisting of as much as 75 per cent dried liver, casein, or beef muscle. Such liver feeding produced granular kidneys in less than a year. Casein produced tubular injury in 16 months, while beef muscle produced changes intermediate between the two. Looking at these results critically one is struck by the fact that a far greater proportion of protein was given to the rats than could possibly be taken by man, and also by the probability that the differences between the effects of the materials fed may depend upon substances associated with the simple proteins, possibly substances arising from nuclear material. Dr. Newburgh has kindly permitted me to mention that further experiments of his, which will soon be published, indicate that the latter supposition is probably true. Substances like liver may produce renal injury if taken long enough and in sufficient amount. It remains to be shown that such injury occurs in man in the amounts which can ordinarily be taken.

On the other hand, we have the testimony of Stefansson as to the absence of injurious effects in the case of the Eskimo who gets 40 per cent of his energy from protein. McClellan and DuBois[14], who recently completed a year of observation of Stefansson and Anderson on a meat-fat diet such as one may live on in the Arctic regions, found no demonstrable injury of

any kind. Also McCay[15] of the Indian Medical Service has testified that the incidence of nephritis is no greater among the meat eating Europeans in India than among the Bengali who get very little good protein.

In the writer's clinic, Dr. Henry Keutmann has carried out some very careful observations of the effect of high protein in the diet on the course of chronic hemorrhagic nephritis. These observations are being published in detail elsewhere. Patients were selected who had come to a fairly constant level of hematuria as measured by the Addis sediment counts[16]. In the following table are compared some of the observations made in a typical case of a boy of 15 years with chronic hematuria following upon an attack of acute nephritis, months before. Comparison is made between the findings during two weeks on a diet containing 75 gm. protein and during four weeks on a diet containing 150 gm.

During the experiment the patient improved clinically, showed no elevation of blood pressure, maintained constant weight and a positive nitrogen balance. The relationship between the urinary ammonia and the total titratable acidity remained unchanged, though both of these were increased 50 per cent when the protein intake was doubled.

Summary

These experiments have convinced us that liberal protein allowances in the diet do not of themselves, injure the kidneys. When the excretory power is nearly at the level of the minimal endogenous protein catabolism, which can be achieved by making full use of the protein sparing qualities of carbohydrate and fat, nothing is gained by reducing the protein intake below the point of nitrogen balance. Full advantage should be taken of the tendency to deposit protein by all individuals who have lost it, either by inanition or by toxic destruction or through albuminuria. Protein which is deposited makes no demand upon excretory functions; it builds up depleted tissue and circulating proteins with beneficial effects upon the course of the disease.

Table I. Julius B.

	75 gm. Protein 14 days	150 gm. Protein 28 days
N.P.N	26-41 mgm.%	26-38
CO_2C.P.	57-60 vol. %	55-74
Serum Proteins	7.2-7.4%	7.5-7.6
Urine pH	5.3-5.5	5.1-5.8
Urine R.B.C.	122-310 (x 10^6 per 12 hrs.)	95-284
Urine Protein	Av. 65 mgm. (per 12 hrs.)	Av. 71 mgm.
Casts 12 hr.	150-697 (x 10^3)	86-284
Urea Clearance	45-64 cc. (C_s)	63-84 cc.

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Mountain Fever and Spotted Fever of the Rocky Mountains–Clinical Studies*

By Noxon Toomey, B.A., M.D., F.A.C.P., *Palmyra, Mo.*

UNKNOWN fevers first encountered by white immigrants in the Rocky Mountain region between 1850 and 1873 have become of constantly increasing clinical interest and public health moment due to recent discoveries of new and widened endemic areas, and to the involved medical problems now more fully appreciated.

Scientific study of fevers in the Rocky Mountain region began clinically in 1880, epidemiologically and pathologically in 1902, bacteriologically in 1906, immunologically in 1908, and preventively in 1911. These studies have so increased rather than narrowed the fields of inquiry that much of what has been written has had to be rewritten from time to time to accommodate the newer scientific facts and observations relative to the spread and increasing knowledge of this disease, or these diseases. So great has been the enlargement of the public health and scientific relations of spotted fever and its congeners within the last four or five years that standard monographs of a few years ago give a very inadequate picture of the economic and medical problems as now known. Hence a comprehensive clinical study, taking into account the newest scientific facts can further perfect the literature of internal medicine.

Of the group of mountain fevers in the western part of the United States we will first consider the component of the group that is now the best known, namely spotted fever, although there is reason to believe that the non-exanthematous, intermittent tick-borne disease (mountain fever) was encountered by white men equally early or earlier than spotted fever. The early history of the intermittent or mountain fever is more obscure because, being non-exanthematous, it was more difficult to unequivocally distinguish it from the other prevailing fevers of the mountains such as malaria and the fevers of the enteroidea group.

Early History of Spotted Fever

Occurring among the Shoshones, Flatheads and Nez Percé Indians of southern Idaho, western Montana, western Wyoming, northeastern Nevada, and northwestern Colorado prior to immigration by Caucasians, *spotted fever of the Rocky Mountains* first occasioned illness among white settlers in 1873. It was first observed by Dr. H. Dressing near Paradise Valley, Humboldt County, Nevada, in 1880, and five years later by Dr. Coughennor

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of Corvallis, Montana. In the same year, 1885, it was observed in Lake County, Colorado, and in 1886 in Mesa County, Colorado. It has, however, only recently attracted notice in those counties although it has apparently occurred there from time to time[164].

Although at first variously diagnosed as 'black measles', cerebrospinal fever, dengue or typhus, from 1880 to 1895 it became apparent to the more observant physicians practicing in the heavily infested areas that they were confronted with an undescribed disease or group of diseases. At that time a modicum of the local practitioners considered mountain fever as distinct from spotted fever, but as the former term was used more loosely than the latter it undoubtedly included some other fevers seen at high altitudes. And yet despite admitted unskilled diagnoses and recognized looseness in the use of the term mountain fever, the idea persisted in the minds of some judicious observers that there was a mountain fever that was not spotted fever, malaria, nor typhoid fever. That fever they considered to be very probably an independent infection.

The prevailing idea of local medical opinion in Idaho, reached prior to 1893, became known to Captain Marshall W. Wood, U. S. A., Post Surgeon of Boise Barracks, Idaho, who reported the current opinion to the Surgeon-General of the Army. On the latter's direction Capt. Wood later obtained brief clinical descriptions of the spotted disease from eight general practitioners. These reports were published in 1896 under the title "Spotted Fever as Reported from Idaho"[1].

The first public discussion of spotted fever and mountain fever was by the Idaho State Medical Society at Boise, Idaho, in 1896 (discussion opened by Dr. William C. Maxey), and by the Rocky Mountain Interstate Medical Association at Salt Lake City in July, 1897. Neither meeting gave rise to published accounts of the discussions[16].

Clinical studies made by the Maxeys, father and son, and reported by the son, Dr. Edward E. Maxey, characterized the main symptomatology of the indigenous spotted fever and served to emphasize that in southern Idaho the disease was more prevalent but not nearly so virulent as in western Montana[2].

Satisfied of the infectious nature of the new and imperfectly studied disease, the first act of the newly organized Montana State Board of Health was in 1901 when it commissioned L. B. Wilson and Wm. M. Chowning to make an epidemiological and pathological study of the indigenous disease, with particular reference to the virulent form in the Bitter Root Valley. Wilson and Chowning in their reports remarked upon mild, febrile cases without an eruption and of unknown nature, but did not make a study of cases of the sort, nor express an opinion as to their nature[8].

The chief permanent results of Wilson's and Chowning's studies were to make the Bitter Root Valley form of spotted fever more widely known, more fully described clinically, and more scientifically established in that their epidemiological studies led them to focus attention on ticks as vectors of the disease, without, however, actually establishing the fact. They described

a piroplasm which they thought they saw in the blood of patients with the virulent form of the spotted fever, and attached etiological significance to it. Later, however, C. W. Stiles and W. W. Welsh recognized these supposed intra-erythrocytic organisms as artefacts[15].

Wilson and Chowning's supposition in regard to a tick as vector of the spotted disease was confirmed experimentally by McCalla and Brereton who in 1905 transmitted the mild, Idaho type of spotted fever to man (two cases) and by King and Ricketts who transmitted the virulent Bitter Root Valley strain of the disease to guinea-pigs by means of tick attachment (feeding) experiments.

The high mortality rate (70 to 90 per cent) and the economic importance of the malignant Bitter Root Valley form of spotted fever so centered the attention of investigators on it that the benign, aberrant and non-exanthematic forms of local fever attracted almost no scientific study, with practically the sole exception of the mild form of spotted fever indigenous to the Snake River Valley in Idaho, which on account of its habitual low mortality rate (5 per cent) had from the earlier days led some to consider that it should be recognized as a separate disease. However, by means of later serologic studies the Idaho form of the disease has been proven to be immunologically identical with the malignant Bitter Root Valley form although amply warranting consideration as a distinct and easily recognizable clinical type, due almost certainly to a fixed difference in the virulence of the local strain of the virus.

As an historical account of the laboratory, and other scientific work done on these fevers since Ricketts first took up the problem in 1906, would have to do exclusively with the exanthematic or spotted fevers peculiar to the Rocky Mountain area, an account of the discoveries connected with them will be deferred until after presenting a discussion of mountain fever.

Mountain Fever

Dismissing the fact that the term mountain fever has been used in almost all languages for whatever zymotic distemper may have prevailed at the time in the high altitudes of the region, it will for our purpose be sufficient to note that the fever under discussion is not implied to have any relationship with the mountain fevers of Europe, India, or any other part of the globe and is used only with respect to the medley of febrile diseases that have laid men low in the Rocky Mountain areas.

As a popular sobriquet for plasmodium infection, *Eberthella typhi* infection, or one of the paratyphoid fevers (including tularemia and brucelliasis), the term mountain fever has perhaps enjoyed most currency in the mountainous West. Connoting nothing to the medical mind, the use of such a term in medical literature is usually regarded as a token of ignorance. Nevertheless the term has a history and a persistency in the West, and it is for us to determine if possible whether by it a separate disease entity has at times been designated.

The earliest professional use in the West of the term mountain fever had to do largely with remittent and inter-

mittent fevers although by some the term was used for the continued fevers, including no doubt tularemia and abortive and masked forms of typhoid fever[3]. Although these reports were grouped by eastern bibliographers and clinicians with the aberrant forms of typhoid fever, the remittent and intermittent character of some of these mountain fevers stands out clearly. Also one is impressed by their comparatively *short duration* (eight to fourteen days), the *seasonal incidence* (April to June), the relation of *protracted chilliness but no chill* to fever, and the admitted *lack of effect of quinine* on them[13]. Furthermore, we know today that in some of the high mountain passes and valleys from which the "brief intermittent fever" was reported, plasmodium infection *must have been absent* in the early days as the necessary vector, an anopheline mosquito, *was not indigenous above the valleys of the plains.*

As in these cases no skin eruption was reported it would not conform to our present conception of spotted fever to regard them as being one and the same disease, nor cerebrospinal fever. That a focal infection (streptococcic or pyogenic), or bronchopulmonary invasion would explain all cases not due to a plasmodium or an enteroidea, would seem most likely, and certainly some cases of tularemia would be confused with the doubtful group. Dengue or influenza perhaps accounted for the "epidemic mountain fever" mentioned by E. P. Vollum, and yet neither of those are apparently the endemic, seasonal, "brief remittents, easily cured" of the north Rocky Mountain region[9]. A brucelliasis (undulant fever) might be the explanation of the mountain fevers of uncertain origin but if so it is extremely difficult to account for army cases being referred to as brief, for brief they must have been, because it is well known that in the army not only are men able to consult a doctor on the slightest pretext but do do so to escape doing duty, hence it is unlikely that any of these army cases much exceeded two weeks, whereas brucelliasis usually runs not under two to four months and usually longer; such a long protracted, low, ambulant fever would become known to the army medical officers in the West, and would have been described as such and not as "brief remittents easily cured". Furthermore we now know that mountain fever is tick borne and not milk borne, and is seasonal whereas brucelliasis is not.

As for bronchopulmonary invasions accounting for these fevers of debatable nature we need have little concern as bronchitis, pleurisy and pneumonia in high altitudes are clear cut, particularly severe, diseases with localizing thoracic symptoms and signs so intense as not to escape the attention of a physician. It is therefore chiefly atypical plasmodial fevers, the focal infections and the zymotic infections of influenzal type that might give currency to an idea of mountain fever as being something apart from the previously recognized types of intermittent or remittent fever.

From none of the early literature on mountain fever in the West, after excluding cases of presumable plasmodium infection or the enteroidea, can anything indisputably defensible from the standpoint of individuality be ex-

tracted, as the focal infections or the zymotic infections of influenzal type can perhaps be invoked to explain the cause of the remaining undefinable cases. And yet through the maze of numerous early but unsatisfactory descriptions of non-exanthematic febrile cases in the Rocky Mountains, one catches glimpses of a brief remittent fever that does not conform to known forms of paludism, the fevers of focal origin, or influenzal attacks of gastro-intestinal or upper respiratory tract type. This fever, after years of comparative study, was eventually characterized as follows: as being seasonal (limited to the spring and early summer months), as being of brief total duration with one to three forty-eight hour remissions with intermissions of two to eight days duration, with pronounced, prolonged chilliness at onset (which was fairly sudden) but without rigor, as being accompanied by constipation and severe muscle aches and pains (chiefly in the back and loins, with headache occasionally) and followed by a quick convalescence but a terminal anemia. Nothing was said about a skin eruption.

Mountain fever was observed to occur only in the spring and early summer months (tick season) and was categorically stated to be different from the autumn and winter fevers. It certainly was what the early practitioners in the mountainous portions of the West had in mind when they refused to ascribe to the eastern dictum that all mountain fevers were either malaria, typhoid fever, rheumatism (focal infections), cerebrospinal fever or influenza. As to the etiology and epidemiology of mountain fever nothing was predicated; certainly ticks as vectors of the disease were not so much as suspected, although now known to be at least one of the vectors.

Due to limitations of space, only two extracts from the early literature will be given verbatim. One is an instructive tabulation of case incidence of mountain fever[11]. Despite the medley of fevers that were confused under the name 'mountain fever' the incidence of cases paralleling the tick season strongly suggests the occurrence of a special tick-borne disease. The second quotation is typical of many reports from army surgeons on duty at Wyoming, Montana and Utah military posts in the early days. This quotation is from the surgeon of a cavalry command of about five hundred men who were, in 1878, marched through the Wind River Canyon of Wyoming, one of the celebrated mountain fever and spotted fever areas of early as well as recent years. Although one man died of typhoid fever, verified by necropsy, the bulk of the cases were acquired over a sixteen day period (four day bivouac and twelve day march through the mountains) at the end of which all were so nearly well as not to require hospitalization on reaching Fort Fetterman. Of these cases Doctor Gray wrote:

"These cases all presented the same general phenomena in the beginning. Invariably the first complaint was that of feeling cold, and 'aching all over'. Then there was lack of appetite, thickly coated tongue, and constipated bowels. The disease was in no instance ushered in with a well marked chill, and during the first twenty-four hours the fever was always light; but there was mental obscuration, sometimes delirium, and more or less inertia, the subjects seeming not to care whether they lived or died, or what

was done with or for them. The patient always admitted a feeling of distress, but never could localize it, except in one case (the man who subsequently died at Fort Fetterman, who complained greatly of pain in his head and the 'back of his neck'). The fever once developed, never after wholly left the patient, but exhibited a decided daily exacerbation, beginning with *chilliness* for a period of half an hour or so, accompanied by cold, clammy sweat, and followed by an intensely hot skin, with small and rapid pulse. These exacerbations generally continued about eight hours, sometimes longer, and then would follow a period of eight or ten hours of lower temperature and comparative freedom from discomfort, during which sleep was possible. There was an increasing, but not a great degree of prostration, as every man was able to ride his horse during the day's march of eighteen to twenty-five miles, and continued to do so daily without assistance until Fort Fetterman was reached. There were wanting the distinctive symptoms characteristic of typhoid, and yet quinia seemed to have no effect to prevent or control the daily return of the high fever, though administered in large doses."[13]

For a most valuable early account of mountain fever we have the report of Captain Charles Smart who strenuously tried to make mountain fever out to be malaria. By his own admission he had to write from Fort Bridger, Wyoming:

"I could not bring myself to record these cases as malarial remittents but put them down as catarrhs and quincies, and awaited developments. These came in a very short time. Cases appeared of fever without any complication by local lesion, and I recognized that I must be dealing with the incipiency of our so-called mountain fever."

He concludes a most careful description of three seasons' (Springs of 1874, 1875, 1876) experience with the non-exanthematous, intermittent, tick-borne (mountain) fever, as follows:

"One point, however, remains to be mentioned. It is that the records of the post, the figures left behind them by my predecessors as embodying their experience of the prevalence of mountain fever, corroborate my own observation, showing the months of May, June, and July to be the months of visitation. Thus, during the eight years previous to my assignment, May gave an average of 5.60 cases per thousand of mean strength; June, 13.89; and July, 9.47; while no cases were recorded during the months of September and October. Yet Dr. Drake reports those very months of September and October as the period of maximum prevalence of malarial fevers in the United States.

The following table shows the average strength of the command and the prevalence of this fever in cases per thousand of mean strength:—

Month	Strength	Cases
January	172	4.36
February	167	.75
March	169	1.49
April	154	1.62
May	134	5.60
June	135	13.89
July	132	9.47
August	145	4.26
September	131	....
October	156	....
November	171	5.85
December	168	.74
Annual	153	48.03

The same author writing of Camp Douglas, Salt Lake City, mentions three cases which "after being discharged from hospital as entirely recovered, made his [their] appearance in eight days with a recurrence of the febrile attack, but it was readily removed by quinia and no subsequent relapse has taken place".

The first account of the non-exanthematous, intermittent tick-borne (mountain) fever that has come to my notice is the following which was writ-

ten by Assistant Surgeon Patzki at Fort Steele, Wyoming Territory, in 1875, and is as follows:

"A remittent fever, occasionally very severe, is met with, by the mountaineers called mountain fever, and much dreaded by them. The most prominent symptoms are headache, severe aching through the whole body, insomnia, furred tongue, frequent full pulse, constipation. Chills are infrequent. The efficacy of large doses of quinine proves the malarial origin. The mountaineers treat it with their panacea, sage tea, and, as they assert, quite successfully. Men cutting timber along the streams, mostly Danes and Swedes, suffer most from this fever."[10]

Before considering the modern writings on the subject of mountain fever we will review the scientific work done on its 'family relation', or perhaps congener, spotted fever of the Rocky Mountains.

The Recent History of Spotted Fever

From 1906 to 1911 the scientific work of H. T. Ricketts, P. G. Heinemann, and associates contributed greatly to a knowledge of the virus, the factors of transmission, the immunological reactions and the morbid anatomy of spotted fever. Later, in 1918, Wolbach added pathological and bacteriologic data and advanced as the causal virus a minute organism, a rickettsia, which he was unable to cultivate except in tissue cultures[146]. Noguchi in 1923 was unable to confirm Wolbach's work but did show that three strains of rickettsia were non-pathogenic and that a filterable virus could be obtained from the vector, *Dermacentor andersoni*. Ricketts and Spencer and Parker were not successful in forcing the virus through a Berkefeld filter[201].

For our present purpose it is more important to note the tick control measures instituted by McClintick and Bishopp and augmented by Fricks; the tick parasites introduced and propagated in Montana by R. A. Cooley [207], who has contributed valuable ecological studies of tick biology and distribution[86]; the accurate statistics of spotted fever maintained by Dr. W. F. Coggswell, secretary of the Board of Health of Montana; and the epidemiological and parasitologic work of R. R. Spencer and R. R. Parker called forth by the spread of the disease since 1914[108, 114,129]. F. L. Kelly[98], J. G. Cumming[109], F. C. Stricker[134], A. B. Tonkin[214] and particularly F. E. Becker[164, 203] have studied spotted fever in its now more widely extended endemic area.

Lately (1931) Rumreich, Dyer and Badger have discovered an eastern and southeastern states endemic area that is believed to have been in existence for at least the past twenty years[218].

Spencer and Parker have introduced a practical vaccine of great preventive value[201]. Since 1925 between twenty to twenty-five thousand persons have been vaccinated with it.

Although the above mentioned studies were undertaken without reference to the non-exanthematic, intermittent tick-borne (mountain) fever, they constitute an invaluable foundation for future work on mountain fever.

Modern Observations on the Intermittent Non-exanthematic Tick-borne (Mountain) Fever

In 1896, from Fort Washakie, Wyoming, Henry I. Raymond described, as typhoid fever, typical cases

of Rocky Mountain spotted fever and also non-exanthematic cases of two to four day fever with one remission lasting two or three days after an intermission of two or three days, and a short 6 to 8 day) total duration[291]. Raymond was apparently unfamiliar with the medical ideas prevailing in Idaho and Montana with respect to spotted fever. His cases were all observed in the tick-season (late April to June) but as he finally regarded his cases as typhoid fever he incriminated the water supply and did not look for an insect vector. His case reports (Cases: W.S., J.P., J.F.S., J.C., F.G.W., and D.A.) leave no doubt that he observed cases of the intermittent, non-exanthematic tick-borne disease later described by Kieffer from a point in Wyoming some two hundred and fifty miles south-eastward. Raymond remarks on the prevailing divergence of opinion among the local practitioners, one of whom (Dr. H. L. Callaway) clearly distinguished his typhoid fever cases from the spotted fever cases, which were then diagnosed as purpura simplex and purpura rheumatica (simplex).

In 1901 Dr. W. W. Woodring of Mt. Pleasant, Utah, before the Rocky Mountain Interstate Medical Association maintained "that there is such a thing as mountain fever, mostly confined to the young and those under fifty. It is ushered in with a chill followed by a temperature of one to four degrees during the following twenty-four hours."[34] (Quoted from abstract in Jr. Am. Med. Assoc.).

In 1902 Wilson and Chowning in writing of spotted fever, which they suspected as being a tick-borne disease, state: "Several physicians, however, recognize in addition a mild type in which there are no spots. There is much difficulty in the accurate diagnosis of the mild type, and though its existence must be recognized yet during the investigation herewith reported, all of the examinations except one were made on cases of severe type. . . . . In Montana cases of the mild type of the disease, which show no spots, are as yet too indefinitely differentiated to permit of their inclusion with those of the severe type which invariably develop the eruption. That such cases exist there can be no doubt. They are never fatal."

It is to the careful studies of Major Charles F. Kieffer at Fort D. A. Russell, Wyoming, in 1906, that we are indebted for the first exact knowledge of an intermittent, non-exanthematic tick-borne disease of short duration and no known mortality. Kieffer prefaced his paper with the recognition that "the older physicians in the Rocky Mountain regions have always insisted that there was a special type of fever indigenous to this section of the country. This fever or, as it appears to me, group of fevers has been given various names, but principally that of mountain fever. The group has simply been dismissed in recent years, although many good observers still hold that there is a type of fever which is neither malaria nor typhoid."[35]

Kieffer recognized two types: one having three to seven recurrences of forty-eight hours duration marked by forty-eight hour intermissions and "another type, but not so common, in

which after the initial chill the temperature rises ladder-like, for two or three days. These cases have more marked prodromes or more marked abdominal symptoms (abdominal tenderness and enlargement of the spleen) and present a clinical picture which is, at first, extremely suggestive of typhoid fever." Kieffer's paper should be read in the original.

After Kieffer's contribution, mountain fever attracted only local interest in Colorado and the adjacent parts of Wyoming and Utah. No notice was taken of it in medical literature until 1926 when F. E. Becker said that "certain symptoms of malaise, not typical of Rocky Mountain spotted fever, frequently follow tick bites in Colorado. Evidence supports the view that they are due to the tick bite, and are not part of the clinical picture of Rocky Mountain spotted fever. Many micro-organisms other than *D. rickettsi* are found in the ticks of Colorado."[164] In a later paper Becker says "An atypical infection following tick bite with characteristic constitutional symptoms, but without a skin eruption, is common in Colorado and is locally known as 'Colorado Tick Fever.' If this is an attenuated spotted fever, the definition of this disease must be modified to include cases without skin rash. Indolent ulcers frequently occur at the site of the tick bite."[203]

In 1929, R. R. Parker wrote "Public Health Service investigators have for several years been interested in a wood-tick-caused condition which occurs quite extensively in portions of Colorado and is far from uncommon in Wyoming. In sections of Colorado this condition has been commonly known as 'mountain fever'. Compared to the usual typical cases of spotted fever it is relatively quite mild, and at the present time it is uncertain whether it is a mild type of spotted fever or a distinct disease entity."[192]

With respect to a Rocky Mountain spotted fever without an eruption, Dr. R. R. Parker in 1930 said ". . . 'spotted fever without eruption'; a diagnosis which we feel is purely presumptive and rarely justified." (Page 95[201].)

From the title of a paper by Dr. F. E. Becker before the Boulder County (Colorado) Medical Society on May 8, 1930, on "Rocky Mountain Spotted Fever with Special Reference to Cases Without Rash," we gain the impression that Becker considers mountain fever and spotted fever to be the same disease but on what evidence we have been unable to learn.

Spirochetosis from Argasidae

In 1930, Burford Weller and G. M. Graham of Austin, Texas, described a group of three cases of a relapsing fever following infestation with the tick *Ornithodoros turicata* acquired by some youths when they explored a cave in the Colorado River Valley, Texas. An unidentified spirochete was found in the blood in all cases, and a similar organism was recovered from a rabbit inoculated through the abraded skin with a crushed tick and thereafter violently ill. Graham, who later visited the cave, was bitten and was ill with a relapsing type of fever, a spirochete being recovered from his blood[83].

Serious constitutional reactions following bites of *Ornithodoros turicata*

(A. Duges) 1876 and *O. talaja* (Guerin-Meneville) 1849, and *O. coriaceus*, (C. L. Koch) 1844, have been known in Mexico for many decades[82]. For the present at least it is not thought proper to consider this argasid spirochetosis as identical with the non-exanthematic, intermittent tick-borne (mountain) fever of the northern Rockies, due to well marked differences in the vectors and the clinical courses of the diseases.

Differentiation of the Two Wood-tick Transmitted Fevers of the Rocky Mountains

Spotted fever is now recognized to follow more different clinical courses than the two classical types described prior to 1908[4,31,41]. However, this fact is not accorded sufficient notice in text-book and clinical literature. Up to 1908 the two recognized types were *the benign (very slightly remitting) type in Idaho,* and the *short but malignant form in the Bitter Root Valley*; the latter (usually without remissions) running a constantly rising febrile course to hyperpyrexia and ending almost invariably in circulatory collapse between the fifth to eleventh day.

A *very mild, ambulant type* with exanthem scanty or evanescent is now not infrequently recognized in Idaho and eastern Oregon. It is said to run a prolonged course (between three and a half to four weeks).

A *moderately severe, protracted, severely emaciating type* of the disease, in which the daily remissions are better marked than in other forms, occurs where the disease is of intermediate virulence as in Nevada, Utah, and Colorado. This type may last four to five weeks and is sometimes called the chronic type.

Inasmuch as there are four readily recognizable clinical types of spotted fever, the different strains of the virus will excite symptoms in somewhat differing intensity and combination. Thus onset may be abrupt or more gradual (but is always reasonably clear cut and never very gradual). The fever may terminate with abrupt or gradual lysis but never by crisis. The fever has a tendency to produce hyperhidrosis early but a dry skin later in the course, but the degree of hyperhidrosis is, as with certain other symptoms and signs, somewhat conditioned by the patient's habitus. During onset, vomiting occurs commonly in the types of moderate and severe intensity, but like some other symptoms is partly conditioned by the patient's habitus, thus occurring in some of the mildest cases and not occurring in some of the most severe. Universal chilliness, without rigor, varying in intensity from distinctly noticeable to marked, almost invariably occurs. Usually the chill (chilliness) is not a shaking, chattering rigor but is more persistent than in other fevers, often lasting three to four hours, and is devoid of 'creepy feelings'.

Stupor is an early and rather constant characteristic of the disease, even in its mildest forms, and a low (only very exceptionally violent) delirium occurs commonly. The tone of the muscles increases rather than lessens (a feature not sufficiently noticed in the literature). This may account for the spastic inability to void. Constipation is usual during the first two or

three days. It seldom gives way to diarrhea. Inability to protrude the tongue and to speak are, in the severer forms, curiously frequent signs after the first few days. Insomnia is always a troublesome feature.

The pulse is characteristically quite rapid (110 to 140) becoming easily compressible in the virulent form. Respirations are normal or slightly more rapid; the respiratory excursion not being reversed. Very pronounced congestion of the conjunctivae without lachrymation is an almost constant symptom in all types of the disease. Muscle aches and pains, especially of the extremities, and chiefly of the flexor groups, occur early, practically at the onset, and may be one of the first symptoms.

The rash, occurring from the end of the second day to the fourth day, may be described briefly as consisting of erythematous (usually somewhat cyanotic) ovoid to pseudomorbilliform, lenticular macules, at first slightly raised above the surface of the skin. The rash first appears on the ankles and wrist and spreads up the limbs to appear on the back and then the abdomen and chest, usually sparing the neck and face, which however commonly takes on a puffed appearance. The rash persists well into convalescence, usually becomes more or less purpuric, and stains from it may last for months. Confluence occurs in severe cases but is not common.

The fever of spotted fever is continued, slightly remitting in the milder cases, or constant to slightly rising in the malignant cases. At onset it usually rises abruptly or sub-abruptly with one or two slight remissions during the first twenty-four hours. The fever may become distinctly remitting after the first few days, and especially quite so in the latter course of the moderately severe, protracted cases but never does it completely abate until the terminal lysis. However, without a distinct undulant type or definite intermissions there are occasional fluctuations in the daily maxima and minima. *Distinct intermittency does not occur in spotted fever* although after the abrupt lysis there may be, following a subnormal temperature for a day, an after-fever of very slight degree and of one or two days duration.

A severe secondary anemia develops after the first week of the disease, and persists well through convalescence, and small gangrenous areas on external genitals, ears, pharynx and sometimes on digits occur as not uncommon terminal complications in the protracted, severe forms.

As for *mountain fever*, with its equally abrupt onset: Besides the well marked intermittent character of the fever, and its brief total duration (eight to sixteen days), and the absence of an exanthem, mountain fever differs from spotted fever in its lack of local symptoms such as conjunctivitis, pharyngeal engorgement, and terminal gangrenous areas. The site of the tick-bite is commonly the site of an indolent ulcer, which is not the case in spotted fever. We note in both a stuporous state and pronounced aches and pains in the muscles, but in mountain fever the latter are referred mostly to the back and loins whereas in spotted fever they are mostly in the

extremities. Insomnia is a troublesome feature in spotted fever but occurs only transitorily or not at all in mountain fever. Constipation and urinary retention due to vesical spasm occur in both diseases, but bronchial irritation is not noted in connection with mountain fever. The pulse, quite rapid in both at the onset, has a very decidedly greater tendency to slowness, even to a distinct bradycardia, in mountain fever than in spotted fever, in which it has a tendency to become very rapid and thready, especially in the severe forms. Convalescence is much quicker and more rapidly completed, often being dramatic, after mountain fever than after spotted fever, which is usually quite protracted. Nothing like so great a secondary anemia is produced by mountain fever compared to the fifty per cent erythrocyte and hemoglobin reduction of spotted fever. The tongue is dry, furrowed and thickly coated from the onset of mountain fever whereas during the first week or ten days of spotted fever it is swollen, somewhat moist and only slightly coated. Drenching sweats seem to be a little more common during the remissions of mountain fever than during the abrupt lysis of spotted fever.

Although the clinical differences between mountain fever and spotted fever could be caused by a difference in the strain of the virus it is our opinion that unless the two diseases are proven to be due to the same virus we have to recognize such a decided dissimilarity in their symptomatology and clinical course as to justify us in regarding them as separate disease entities.

The Relationship of Spotted Fever and Mountain Fever

Not until the immunologic relations of one disease to the other have been established will we have a secure basis for uniting these diseases or recognizing them as etiologically separate entities. Clinical study has gone about as far as it can. From the present observational aspect, the intermittent, nonexanthematic tick-borne disease has only one thing in common with spotted fever and that is the fact that it can be transmitted by the same species of tick. So also can tick paralysis and tularemia be transmitted by *Dermacentor andersoni*, and yet it is patent that they are different diseases from spotted fever, etiologically as well as clinically. Thus the fact of a vector common to spotted fever and mountain fever should not compel us to group them together, except perhaps as an epidemiologic expedient. For statistical purposes it would be eminently unwise to consider them the same disease, and this after all is one of the most practical tests.

By what means mountain fever will be more intimately compared to spotted fever we can not now predict, as it is not a serious disease and is not attracting scientific study. What we should learn is whether or not those who have had the intermittent, nonexanthematic tick-borne disease are immune to spotted fever. Obviously it would not be prudent to use a strain of spotted fever more virulent than the Snake River strain for a tick feeding experiment on one who had mountain fever but was known not to have had spotted fever. There are other

methods for testing the relationship. Blood drawn during the height of the intermittent, non-exanthematic disease can be injected into guinea-pigs immune to spotted fever and into those susceptible to spotted fever, and into men who have had and who have not had spotted fever, provided the donor is known to be not syphilitic. To try to give the benign disease, mountain fever, to one immune to spotted fever by means of a tick attachment (feeding) experiment would be inconclusive if only negative data were acquired, as it would be extremely difficult to prove that the ticks used were virulent for mountain fever at the time of the attachment. The virus does not occur in all wood-ticks and its successful transmission is influenced, perhaps, by phases of latency or other conditions. If the non-exanthematic, intermittent tick-borne disease can be established in a laboratory animal it is important that it be done so that the virus can then be transported more readily and maintained for study with greater certainty and convenience.

Summary

For seventy-five years many physicians practicing in certain parts of the mountainous West have recognized a brief, seasonal, non-exanthematic, remittent fever with certain characteristic symptoms and no known mortality, which they have considered indigenous to the locality and different from typhoid fever, malaria or other known diseases, although confused with malaria or typhoid fever by some.

The early published reports are not absolutely conclusive but a review of them leaves the impression that there were early observed cases of a fever, called mountain fever, that conformed to our present knowledge of the disease, and remain inexplicable on the basis of a plasmodial, enteroideal or undulant infection.

A seasonal, non-exanthematic, remittent (occasionally continued) and intermittent fever of short duration and no known mortality, and conforming to the conception of mountain fever as understood in certain parts of the Rocky Mountain region was associated by Kieffer with a transmission by means of the bites of wood-ticks.

The virus of mountain fever has not been studied and the immunology of the disease with respect to spotted fever is not known.

The tick-borne, non-exanthematic mountain fever has a clinical course characteristic and peculiar to itself and one not difficult to distinguish in the aggregate.

For clinical or statistical purposes it would be exceedingly unwise to identify mountain fever with spotted fever or undulant fever.

Until its course is identified or the immunological relationships of the disease are clearly established, mountain fever should be considered to be a distinct disease entity.

Nosologically the tick-borne mountain fever resembles the dengue group of fevers somewhat more closely than the relapsing (spirochetal) fevers. The name American Mountain Tick-fever is proposed for it.

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American Mountain Tick-Fever and Spotted Fever of the Rocky Mountains–Comparative Epidemography*

By Noxon Toomey, M.D., F.A.C.P., *Palmyra, Mo.*

PARALLEL study of mountain fever and spotted fever affords a most useful method for ascertaining their characteristics, for establishing comparisons and differentials between them, and for determining their respective positions in the social, economic and medical life of our times. Indeed, one might be led to take for granted that inasmuch as both diseases have the same arthropod vector, epidemiology, parasitology and prophylaxis would be identical for the two. Such is true to a large extent but as the diseases do not absolutely conform in the mechanics of their pathogenesis, it is important to compare them in a way that will visualize the differences in their pathodynamics. A common factor or foundation for the two diseases is found, but for each there is a separate superstructure indicating individuality. These differences reinforce our clinical observations concerning the dissimilar nature of spotted fever and American mountain tick-fever.

As very much more is known of spotted fever than of mountain fever it is not possible in the present state of our knowledge to compare the two diseases in all respects. As it is important, however, to give the most complete picture possible of the epidemiology of spotted fever, important features of the latter will be discussed even when the comparable features of mountain fever are not known. Thus not only will spotted fever be made known more comprehensively but for the further study of mountain fever various suggestive viewpoints will be presented for elucidation.

Epidemiology

Spotted fever is not contagious nor inoculable from man to man by means of customary contacts. The virus can, however, penetrate the unbroken skin and has been known to do so under exceptional circumstances, such as in the handling of ticks in experimental work[187]. Several laboratory workers have contracted the disease from handling infected material such as tick viscera, tick eggs and tick feces[195].

Concerning the artificial inoculability of *mountain fever*, no data is available. From the fact, however, that the virus does not have as great a latent, non-virulent, immunity-producing phase as the spotted fever virus, and as mountain fever has been known to occur in larger outbreaks than spotted fever, it

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seems that the virus of mountain fever has a greater certainty of transmissibility through the skin than that of spotted fever.

For neither disease do fomites need be taken into practical consideration although it is not impossible that active virus persists for some days in dead tick material, and that the latter can be spread by fomites under extremely exceptional circumstances.

Distribution. Mountain fever is limited to an area within that of the spotted fever tick-area. According to present knowledge the inference is justified that the distribution of mountain fever is conditioned by most factors influencing the distribution of spotted fever and also by a factor peculiar to itself.

Spotted fever is known to occur in the mountain fever area but in that area it is not quite as prevalent as in other portions of the *D. andersoni* distribution area. Thus, along the axis extending diagonally from the center of the State of Washington southeastward to the southeast corner of Colorado, and for a hundred miles on either side, the spotted fever occurs far more preponderatingly over the northwest two-thirds of this area, whereas mountain fever is limited (approximately) to the southeastern one-third. That the difference is not due to a change in the type of one and the same disease is evident from the fact that spotted fever when it does occur in the southeastern portion is clinically quite distinguishable from mountain fever and is substantially true to its type as existing in the north-west part of its area, although causing somewhat more violent abdominal symptoms when occurring in the southeastern portion of its area[26,178].

Spotted fever occurs in a western, Rocky Mountain or major endemic area; a minor or eastern-southeastern states endemic area, and sporadically elsewhere.

The eastern area is from the southern border of New York to the northern border of Florida and from the Atlantic coast line westward to the Appalachian mountains.

The western endemic area includes the southeastern quarter of Washington[136], the eastern half of Oregon[191], several counties on the northern and (north) eastern border of California[180], all of Idaho except the extreme northern tip, all of Montana[13,195], all of Wyoming[135], the northern half of Nevada[28], the northern four-fifths of Utah[59], and the western three-fifths of Colorado. A characteristic is the especial prevalence of the disease in certain localities (valleys) of the area.

In the above described area mountain fever is definitely known to occur only in approximately the lower and somewhat eastern half, namely in Colorado, Utah, Nevada and Wyoming, although it seems to occur to a limited extent somewhat northwestward of the main endemic area, namely in the southern portion of Idaho and Oregon. However, the northern portion of the *D. andersoni* distribution area, namely Montana and the adjacent parts of Idaho and Washington have not been sufficiently investigated for mountain fever. Mountain fever has not been reported from the eastern-southeastern states endemic area of spotted fever.

Recent Spread. For *spotted fever* the area of known distribution has increased greatly since 1904, and particularly since 1914. It is indubitable that spotted fever has lately occurred for the first time in areas where medical men were sufficiently skilled to have recognized it had it occurred at an earlier date[115]. For instance: in

Montana, until 1914, infection was definitely known in but four counties; Missoula, Ravalli, and Granite, west of the continental divide, and in Carbon county, bordering Wyoming in the south portion of the eastern part of the state. It has now been reported from thirty-one counties in the eastern portion of Montana. It has spread to South Dakota (first reported case in 1915), to North Dakota (first reported case in 1919) and Nebraska (first reported case in 1931)[215].

Maver and others have shown that spotted fever can be transmitted by ticks other than *D. andersoni*, and as ticks that bite man are widely distributed over the United States, Canada and Mexico it is not improbable that spotted fever will eventually have a wider area of distribution.

As ticks do not migrate for any appreciable distance the recent sudden spread of ticks containing virus is probably to be partly accounted for by interstate commerce in live-stock, particularly in sheep, to the wool of which ticks cling for several days before being killed by the sheep's grease. However it would not be correct to suppose that the spotted fever area has been widened solely through the agency of man (commerce, etc.) as the area has undoubtedly been widening slowly through the migration of infected rodents, by means of the rabbit-tick, and the widening dissemination of infected tick eggs by natural means.

It is interesting that the spread of spotted fever to the plains areas of Montana and Wyoming has not (according to available reports) carried mountain fever with it, notwithstanding that the western half (particularly the southwestern quarter) of Wyoming has for years been heavily infested with mountain fever. In fact, by comparing early reports with the present known distribution of mountain fever, *the area of mountain fever appears to have diminished in extent.* This has occurred in the more densely inhabited (cultivated) portions of Colorado and Wyoming, and partly in the Black Hills, and is undoubtedly to be accounted for by the clearing of underbrush and the other tick-eradicatory measures incidental to intensive farming, whereas the virus does not seem to be spread among rodents by the rabbit-tick.

Seasonal Characteristics. Both spotted fever and mountain fever are seasonal diseases being limited by the occurrence of predatory wood-ticks and dog-ticks in nature. The tick season is from the first warm days of spring (March) to somewhat after the maximum heat of summer (about the middle or end of July) although cases have been known to occur not uncommonly as late as September, and rarely at other times of the year. The majority of cases occur in April, May and June, especially in May. Obviously there is some variation from year to year according to climatic conditions, and also the seasonal range varies for different localities according to their latitude, altitude and exposure to sun, wind and rain-fall[78].

Both spotted fever and mountain fever have been observed in rare instances during the cold weather of late winter (middle of December to end of February). This exceptional seasonal incidence can be accounted for by dwellings having become infested

with virulent ticks during the preceding summer or autumn. Hibernating through the winter, these ticks in the dwellings become stimulated to activity at a date earlier than usual by the dwellings becoming over-heated.

Climatic conditions as factors in tick prevalence are important as they operate directly on the life-cycle of the tick and on the pabulum that supports the tick[87]. Thus moderate warmth with moderate moisture and protection from abundant sun glare are the optimum conditions for the wood-tick, any departure in either direction diminishing their prevalence.

Whether there is a distinct difference between the climatic requirements of mountain fever and spotted fever cannot be asserted with full assurance as too little is known of mountain fever, but such data as are at hand seem to indicate that mountain fever is found in a higher and drier climate than is spotted fever, and that it has a longer seasonal incidence (cases being observed not uncommonly in August and early September) which may mean that the virus of mountain fever is more resistant to heat or sunlight, or both, than that of spotted fever.

Geophysical Characteristics. Formerly much significance was attached to spotted fever being particularly prevalent in certain deep, isolated mountain valleys characterized by a spring freshet or water-shed from the melting snows on the upper mountain reaches[7, 19]. These spring freshets serve to increase the prevalence of the disease by irrigating the underbrush in which the ticks hibernate and by washing the ticks down to the foot-hills. Sage-brush favors tick development but any area of woods with underbrush that is fairly dry the greater part of the time, and shaded from constant direct sun glare can become heavily infested. Areas subjected to constant or periodically recurring strong wind currents are not so favorably situated for harboring heavy tick infestation as are the protected sides of the valleys, and this is why the protected sides of valleys are more morbific than the exposed sides.

Relation to Flora. For *spotted fever* the endemic area is not conditioned by the topographical distribution of a special plant or plant relationship, although underbrush, particularly sage-brush, seems especially agreeable to the wood-tick[74].

Mountain fever is much more prevalent in wooded areas than in sage-brush plains and may tentatively be said to be confined to the upper timber regions of mountain passes and canyons.

Relation to Fauna. That *spotted fever* is indigenous to small rodents, particularly chipmunks, was confidently anticipated early in the study of the disease[52], but the latest serologic work has shown that while it does occur naturally among wild rabbits, ground squirrels, woodchucks and probably other small rodents (which act as the natural reservoir), it is actually a rare disease among them, and usually benign. These animals become more or less healthy carriers and are largely responsible for maintaining the disease in nature. Hence rodent extermination is a necessary part of any plan for exterminating the disease. The large wild animals, elk, deer, and mountain goat, and the large domestic animals,

horse, cow, sheep and dog are immune[112].

That *mountain fever* is more especially related to the mountain goat and mountain rat than the gopher and wild rabbit populations has not been proven but seems likely from the character of the localities where it is most endemic.

For both diseases, infection of man may occur at any time of the day or night, and is not especially favored by any part of the diurnal cycle.

Age Incidence. In sections where families live in infected districts there is no characteristic age incidence for either mountain fever or spotted fever. Actually, however, cases are far more common among adults than among children, and this is especially true for mountain fever. This difference in age incidence is largely due to increased exposure to wood-ticks by reason of the occupations of the adults which occasion them to enter the wooded mountain sides as trappers, rangers, surveyors, miners, lumbermen, etc.[121].

Sex Incidence. Differences in exposure to ticks by reason of occupation result in many more cases occurring in men than in women. Cases in women are often caused by ticks brought home by the men and boys of the household.

Occupational Incidence. Spotted fever occurs mostly among persons engaged in agricultural pursuits, and except under special conditions is most common in persons associated with the various phases of the live-stock industry, especially the handling of sheep. Cases also occur, however, among forest service employees, prospectors, hunters, and others whose occupation, or the pursuit of pleasure or profit, takes them into tick-infested sections[165].

Mountain fever is associated more decidedly with the timber industry, hunting and trapping in the mountains, and other mountain pursuits, and in this respect it differs distinctly from spotted fever. Among the early reports of army surgeons in the mountainous West, mountain fever was commonly referred to, whereas spotted fever was observed only rarely, and in certain circumscribed localities (Wind River Valley, Bitter Root Valley, etc.).

Economic Importance. Mountain fever has no economic importance other than that which attaches to any benign fever of short duration. With *spotted fever*, however, it is vastly different. No one who is not in close contact with the spotted fever situation can appreciate the degree to which spotted fever is dreaded in the sections in which it is endemic. Before the commencement of the tick season many fertile mountain valleys become temporarily depopulated, most families moving out until after the middle of July. Naturally such hazards and necessity for inconvenience depress property values and hamper development. The mental worry to which tens of thousands of families are subjected each year during the tick season restricts the enjoyment of the opportunity for out-door life which constitutes one of the greatest natural assets of the Rocky Mountain region. Because of the far greater number of persons involved, these considerations far outweigh the economic loss due to the actual occurrence of human cases. The latter is a serious concern, since, even though recovery occurs, there is a more

or less protracted period of convalescence, often of several months, during which it is often impossible for the patient to resume his usual occupation[187].

The marked prevalence of spotted fever among sheep herders and others concerned with range management of sheep is frequently a real problem for wool growers, and in some sections is a factor which merits and receives serious consideration[91,104].

The Virus in Nature

Reservoirs. Investigations in Montana have shown the following rodents to be susceptible to spotted fever: the Columbian ground squirrel, *Citellus columbianus;* the side striped squirrel, *Callospermophilus leurcurus cinerascens;* the woodchuck, *Marmota flaviventer;* the pine squirrel, *Sciurus l. richardsoni;* the white bellied chipmunk, *Eutamias q. umbrinus;* the yellow bellied chipmunk, *Eutamias b. luteiventris;* the wood rat, *Neotoma cinerea;* the snowshoe rabbit, *Lepus bairdi;* the cottontail rabbit, *Sylvilagus nuttali;* the white tailed jack rabbit, *Lepus t. campanius;* the prairie dog, *Cynomys l. ludovicianus* (Ord); the badger, *Taxidea taxus* (Schreber); and the weasel, *Putorius arizonensis.*

Character of the Virus. The virus of *spotted fever* has been described as having two phases, a non-virulent phase capable of producing immunity but incapable of producing clinical manifestations of infection, and a virulent phase that causes the clinical manifestations of spotted fever and also a permanent (or a long lasting) immunity. This bi-phasic character of the virus is the probable explanation of certain features of the disease that were for long inexplicable. However, the biodynamics of this character of the virus have not yet been elucidated. The virus of spotted fever does not pass through a Berkefeld filter.

The virus of *mountain fever* seems not to have any biphasic character. It possibly can be identified with the filter passing virus recovered from the wood-tick (*D. andersoni*) by Noguchi.

Virulence. Mountain fever does not differ *greatly* in virulence from year to year *or with respect to the locality where acquired.* There are minor variations in the clinical course of the disease in different outbreaks and there are two main varieties of clinical type, the relapsing type and the typhoidal type. Several clinicians have, however, remarked upon the great similarity of all cases of American mountain tick-fever as observed in a given epidemic.

Spotted fever is unique in the fact that the virulence varies greatly in different localities but that the virulence of the infection in any locality is reasonably constant. The areas of greatest known virulence are the west side of the Bitter Root Valley in western Montana, a small section on Kirby Creek near Thermopolis, in Hot Springs County, Wyoming, and an area in the Wind River mountains in Fremont County, Wyoming. In these sections the mortality is high, not infrequently reaching 80 to 100 per cent. The area of mildest infection is in the Snake River Valley in southern Idaho, where the mortality seldom exceeds five per cent. Areas of intermediate severity occur in other sections of the Rocky Mountain region. Ambulatory cases

are not uncommon in southern Idaho and eastern Oregon.[187]

Mechanics of Transmission. For both mountain fever and spotted fever the method of transmission is grossly the same, namely a fixation (bite) of a virulent tick in the human skin for the purpose of engorgement. In the instance of both diseases the virus is transmitted not mechanically, or by the feces, but in the suctorial juices inoculated by the tick during the process of engorgement. There are, however, slight time differences between spotted fever and mountain fever. In spotted fever the tick, even though potent with a highly virulent strain of spotted fever, does not become infective under one and three-quarter hours of fixation. The high proportion of non-immunes infected during certain epidemics (from one-fourth to one-half) leads to the inference that so long a time for infectivity to develop is not present in mountain fever.

Actual and Possible Vectors

Spotted fever is known to be transmissible to man by means of the following species of ticks: the western wood tick, *Dermacentor andersoni*, Stiles, 1908[152]; the California tick, *Dermacentor occidentalis*, Marx; in Utah by *Parumapertus marginatus;* by *Dermacentor albipictus*, Packard; in the northern plains by *Amblyomma americanum* (Linnaeus); and in the eastern-southeastern states by the dog-tick, *Dermacentor variabilis* (Say) Banks, 1908. These ticks also feed on small rodents. No infected *D. albipictus* have been recovered from nature in spite of repeated tests.

Haemaphsalis leporis - palustris, Packard, a rabbit-tick, feeds on all species of rabbits and on game birds but is known not to feed on man. It is, however, a potent and very serious factor in spreading spotted fever in nature, and indirectly in spreading the disease to man.

It is not impossible that ticks unstudied from this aspect, such as the animal (and human) ear tick, *Otiobus megnini*, Duges, 1883, and other species of the Argasidae may some day be found to transmit spotted fever to man.

Whether spotted fever can be transmitted by species of the Clinocoridae (bed bugs) or the Siphonaptera (lice) has never been proven or disproven.

Nymphs of *D. andersoni* have twice been known to infect infants, but usually only adult ticks are known to feed on man. The disease has been transmitted to small rodents by means of larval and nymphal ticks, and these are not uncommon vectors under natural conditions.

American mountain tick-fever is not known to occur outside of the distribution area of *D. andersoni*. In fact it does not occur over the whole of the *D. andersoni* distribution area, the northwestern half of the latter apparently not being concerned with mountain fever. In this connection it is well to note that the common wood-tick of Idaho and Nevada had early an uncertain taxonomic place, at one time being confounded with *D. occidentalis*, and at another time being set up as a separate species, *D. modestus*. Thus, varietal differences within *D. andersoni* apparently occur, but whether the western variety, *D. andersoni var. modestus* is incapable of transmitting

mountain fever remains to be proved.

Whether under natural or laboratory conditions the virus of mountain fever can be transmitted to man by an arthropod other than *D. andersoni*, remains to be ascertained.

Incidence of Tick Virus in Nature. In endemic areas of *spotted fever*, only about one out of every two hundred ticks caught at random are virulent for spotted fever.

What proportion of the ticks in an endemic area of *mountain fever* are able to infect man is not known, but from the rapidity with which some epidemics of mountain fever develop, and the high percentage (twenty-five to fifty per cent) of cases among known non-immune groups, it would appear that most ticks in mountain fever endemic area are able to transmit mountain fever to man.

Morbidity Statistics

Spotted Fever. The morbidity rate varies for different localities, and in a given locality to some extent from year to year, although the virulency in any given locality is reasonably constant. The following table gives the number of cases reported to the Boards of Health in the States and years indicated.

No statistics have been published as to what per cent of the population in an endemic area have an acquired immunity, but in the southern part of Idaho a very large per cent of the sheep herders are known to have recovered from the mild form of spotted fever.

As to *mountain fever* we have no abundance of satisfactory records concerning morbidity, but in certain portions of western Colorado, south-western Wyoming and north-eastern Utah, mountain fever undoubtedly has a very high morbidity rate. Major Kieffer wrote of it as though it occurred commonly at Fort D. S. Russell (south of Cheyenne, Wyoming), but gave no statistics.

At Fort Bridger, Wyoming, Capt. Charles Smart, U. S. A., found that over an eight year period of time a military command with a mean strength averaging 145 men for the six months (March to August), had cases per

Table 1
Number of Cases by States and Years

	1915	'16	'17	'18	'19	'20	'21	'22	'23	'24	'25	26	Total	Annual Avg.
Idaho	360	151	154	103	165	170	204	168	(Extended to)				2210	184
Wyoming	61	27	15	4	6	20	3	77	27	34	37	110	421	35
Nevada	8	20	14	4	2	4	9	1	13	0	11	0	86	8
Montana	42	21	21	10	12	25	27	58	48	44	31	32	371	31
Oregon	53	27	22	13	32	36	45	68	32	13	23	29	393	33
Utah	35	34	15	5	10	9	8							
Colorado	14	5	6	1	2	8	2	11	6	6	4	0	65	6
Washington	8	3	5			2	3	5	1	5	1	1	34	3
California	12	11		3	3	3	11	5	3	6	3	3	63	5
South Dakota	3							3	1		2	2	11	
North Dakota					1		1					1	3	
Total	596	299	252*	143*	233	277	313	395						

*This recession was probably due in part to the abstraction of men from infested areas by reason of military service during the World War.

TABLE 2

Rates per 100,000 *of Population* (1915-1926).

States with state-wide or nearly state-wide distribution		
Idaho, 42.66	Wyoming, 17.00	Montana, 5.64
States with half or nearly half state-wide distribution		
Nevada,	10.33 or for affected (Northern) portion	21.00
Oregon,	4.05 or for affected (Eastern) portion	8.00
Utah,	3.68 or for affected (Northern) portion	7.50
Colorado,	0.63 or for affected (Western) portion	1.50
Washington,	0.22 or for affected (Eastern) portion	0.50
States with approximately one-tenth state-wide distribution		
California,	0.30 or for affected (North-east) portion	3.00
South Dakota,	0.15 or for affected (Western) portion	1.50

thousand of mountain fever as follows: in March, 1.49; in April, 1.62; in May, 5.60; in June, 13.89; in July, 9.47, and in August, 4.26; totaling 36.33 for the tick season; or an incidence of 5.2 cases a year for a command of 145 men. The rate of 3633 per hundred thousand is 85 times the Idaho, or maximum known morbidity rate for spotted fever. Fort Bridger was undoubtedly a heavily infested locality where the men were well exposed and where the varying composition of the command from year to year gave little opportunity for the population to become stable and immune. Errors in diagnosis may have increased the rate somewhat but not enough to raise it 85 times above the state-wide Idaho rate. Indeed, that only five cases a year were diagnosed as mountain fever is excellent evidence that rheumatism, bronchitis and other common ailments were not called mountain fever just because observed at high altitudes, as has been alleged by some.

In Colorado the reported cases of mountain fever slightly exceed those of spotted fever but the comparison is very misleading as most cases of spotted fever are reported, but undoubtedly a small part only of the cases of mountain fever owing to their being benign and frequently overlooked or incorrectly diagnosed.

MORTALITY STATISTICS

Mountain fever has no known mortality.

TABLE 3

Recent Montana Statistics

Year	No. of Cases	Deaths	Mortality Rate
1922	58		
1923	48		
1924	44		
1925	31	10	33%
1926	32		
1927	35	5	14%
1928	29		
1929	20	7	35%

Annual average (whole state) 1914 to 1928: 31 cases per year, average of 9 deaths per year. From 1917 to 1926 there were 369 cases with 89 deaths, or a death rate of 40.34 per cent. Mortality rate for Bitter Root Valley, 1916-1918; children, 50 per cent; adults, 84.91 per cent; all cases, 76.81 per cent.

Spotted fever: prior to 1910, statistics were available only for Idaho and Montana. The best available statistics gave for Idaho a rate fluctuating from year to year between 4 per cent and 7 per cent (Maxey's average, 4.86 per cent) and for Montana (Bitter Root Valley) from 40 per cent to 70 per cent with occasional annual extremes of 35 per cent to 100 per cent.

Next to Montana in order of mortality: Wyoming (1922-1926) 22.80 per cent; Colorado (1913-1926) 18.18 per cent; Oregon (1913-1926) 17.28 per cent; Nevada (1911-1926) 11.81 per cent; Washington (1912-1926) 11.11 per cent; California (1903-1926) 10.53 per cent; Idaho 4.86 per cent. Average (uncorrected) 19 per cent; corrected by weighting, 12.4 per cent. Mortality rate among American Indians (as reported by Dr. Welty): Arapahoes, 20 per cent; Shoshones, 16.6 per cent.

The annual loss of life from spotted fever in the western endemic area now closely approximates one-eighth (12.5 per cent) of 600 cases a year, or between 70 and 80 deaths annually. With the addition of the deaths from spotted fever in the eastern-southeastern states endemic area the total for the whole country is about 100 to 110 deaths annually.

The mildest infection is in the Snake River Valley in Idaho where the mortality seldom exceeds 5 per cent.

Within the eastern-southeastern states endemic area at least 93 cases were known to occur in five states and the District of Columbia in the Spring and Summer of 1930 with 21 deaths—a case fatality rate of 22.6 per cent. In the Rumreich-Dyer-Badger selected series of 50 cases, there was death of seven patients or 14 per cent.

The areas of greatest virulence are on the west side of the Bitter Root Valley in western Montana; a small section of Kirby Creek near Thermopolis in Hot Springs County, Wyoming, and an area in the Wind River mountains in Fremont County, Wyoming. The mortality in these sections not infrequently reaches from 80 per cent to 100 per cent. In southern Idaho near Soda Springs, an area of 100 per cent mortality was formerly known, but no cases have been reported since 1903. A group of very virulent cases was reported from Boise, Idaho, in 1929.

Of five consecutive cases occurring as laboratory infections among unvaccinated laboratory workers, all died.

Summary

The epidemography of two tick-borne diseases, each clinically distinguishable from the other, is found not to be conformable in all respects.

The mountain or more benign fever has been reported only from an area within the range of distribution of spotted fever, but it has not been observed over the whole of the spotted fever area of the Rocky Mountain region, nor is it known to occur in the eastern-southeastern states area of spotted fever.

Mountain fever is apparently limited by barriers peculiar to itself as it has not recently spread, or been carried, into new localities as has spotted fever. In fact, while the distribution area of spotted fever is slowly spreading, that of mountain fever is apparently less than it was formerly.

American mountain tick-fever is predominantly acquired within the upper timber reaches of the mountain valleys, and for the most part at a distinctly higher altitude than spotted fever, which is a disease of the valleys and inter-mountain plateaus whereas mountain fever is most prevalent in the timbered regions and high mountain passes.

A longer seasonal incidence is observed for mountain fever than for spotted fever.

Mountain fever has, in ratio to population, a very much greater prevalence than the largest morbidity rate known for spotted fever, which fact may indicate either a greater tick infestation ratio or that the virus of mountain fever is not subject to a phase of latency as is that of spotted fever.

Spotted fever is a seriously incapacitating disease with an average mortality of 12.4 per cent, and great economic importance, whereas mountain fever is a benign disease of no known mortality and trifling economic importance.

Neither the virus nor the natural reservoirs of mountain fever are known but from data at hand it seems reasonable to suspect that rabbits, spermophiles, prairie dogs and chipmunks are immune to the disease, and that the reservoir should be looked for in mountain rats, badgers, and probably squirrels.

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Thrombo-Angiitis Obliterans Among Persons Past Middle Age*†

By Bayard T. Horton, M.D., F.A.C.P., and George E. Brown, M.D., F.A.C.P., *Rochester, Minn.*

THROMBO-ANGIITIS obliterans usually occurs among men between the ages of twenty-five and fifty years. In a recent study of 150 proved cases by Brown and Allen the youngest patient was aged seventeen years and the oldest sixty-four; only two in the series were more than sixty years. Four other patients have since been observed at the clinic: a woman aged sixty years[2]; a man aged sixty-three years with involvement of the left hand and both lower extremities; a man, aged sixty-five years, who gave a typical history of intermittent claudication in the arches and muscles of the calf for a period of thirty years, and a man, aged seventy-three years, the oldest patient with this disease observed at The Mayo Clinic, and, so far as we know, the oldest proved case on record.

With early diagnosis, improved methods of treatment, and the prophylactic measures which are being carried out in these cases, it is highly probable that a larger percentage of patients will reach the later decades of life without amputation. It is common to find arteriosclerosis of the extremities of patients aged from fifty to sixty years; combined lesions of thrombo-angiitis obliterans and arteriosclerosis are also commonly found in this age group, and either lesion may predominate in a given case. Patients with thrombo-angiitis obliterans in the sixth and seventh decades of life represent a very small percentage of the total number with this disease, as is evidenced by the fact that only six patients aged more than sixty years were observed in a series of more than 500.

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†From the Division of Medicine, The Mayo Clinic, Rochester, Minnesota.

Report of Cases

Case 1. A man, aged sixty-three years, registered at The Mayo Clinic June 4, 1926. His chief complaint was pain in the left foot. His health had always been good. He had been an excessive user of tobacco for many years. Five years prior to admission small painful, raised reddish and bluish lumps along both legs developed. With rest, the condition cleared in two or three months. Two years later pain, tenderness and swelling of both legs developed. This had disappeared, by rest and elevation of the extremities, at the end of two weeks. In September, 1923, an ulcer appeared on the fifth right toe. It failed to heal and caused excruciating pain. The toe was amputated in February, 1924. The wound healed promptly and the patient went back to work feeling perfectly well and remained well until May or June, 1925. At this time a sore spot appeared on the distal plantar surface of the left foot, associated with intermittent pain.

He continued to work most of the time until October 1, 1925, when a painful ulcer developed between the fourth and fifth toes, which did not heal. All of the toes on the left foot were amputated October 30. There was incomplete healing, and two discharging sinuses were still present at the time of admission to the clinic. Considerable pain was present. He had had intermittent claudication pain in the arch of the right foot for eight months. He had had weakness in the left hand for three months, when he attempted to work. Paresthesia was not observed.

The general examination was essentially negative, except for the condition of the extremities. The systolic blood pressure was 136 and the diastolic, 90, in millimeters of mercury. The right radial and ulnar arteries pulsated normally, but pulsations could not be felt in the left radial and ulnar arteries. Definite postural color changes in the hands were not observed. Small pulsations could be felt in both femoral arteries, but pulsations were absent in both popliteal, both dorsalis pedis and both posterior tibial arteries. There were two small draining sinuses in the stump of the left foot. With the feet elevated, there was pallor, graded 1 to 2 of the right foot and graded 3 to 4 of the left foot. When the feet were lowered to the dependent position, there was rubor, graded 3, of the toes of the right foot in thirty seconds, and rubor, graded 4, of the left foot in three minutes. This indicated a slow return of blood to the left foot. Both feet felt cold. There was atrophy, graded 1, of the left thigh and leg. The neurologic examination showed a decrease in sensation of touch, pain and temperature, graded 2 to 3. The other neurologic data indicated arteriosclerosis of the central nervous system. Examination of the

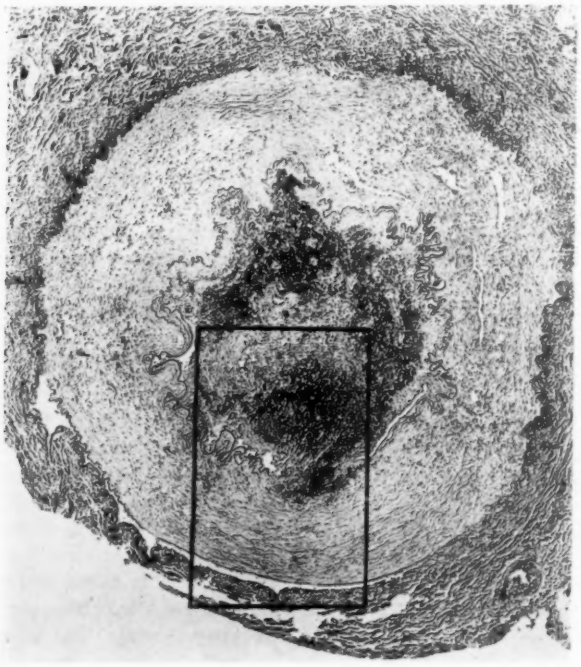

FIG. 1. Cross section of the posterior tibial artery at the level of the ankle. The lumen is occluded by a recent partially organized cellular thrombus, in which lymphocytes and endothelial leukocytes are the predominating cells. A few polymorphonuclear leukocytes are present. Calcification of the wall of the vessel is not present (hematoxylin and eosin stain x 35).

urine and the Wassermann reaction of the blood were negative. The hemoglobin (Dare) was 70 per cent; erythrocytes numbered 4,310,000, and leukocytes 9,700 in each cubic millimeter of blood. The concentration of urea was 34 mg. for each 100 c.c. of blood, and the creatinine 1.1 mg. The glucose tolerance test was negative. The return of phenolsulphonphthalein was 45 per cent in two hours. Roentgenograms of the legs were negative for calcified vessels.

One intravenous injection of triple typhoid vaccine was given, with a rise in systemic temperature of 3.6° F., but there was no rise in the surface temperature of the feet. Because of the patient's age, the severity of the pain, the prolonged healing with draining sinuses, and the absence of a rise in surface temperature in the left foot following the typhoid vaccine, amputation of the left leg was advised, but was refused. The patient went home eight days after admission.

Four months later the patient's home physician stated that the two sinuses had closed approximately half; he felt that amputation of the left leg was advisable. In July, 1927, the patient wrote that one sinus had entirely closed and that the other one had practically closed. He was free from pain and had gained 21.5 pounds in weight. He stated that a good pulse could be felt in front of the left ankle. In July, 1929, he again wrote that his general health was excellent and that the left foot had entirely healed. The foot still felt tender, but he was able to walk with the aid of a crutch.

A diagnosis of thrombo-angiitis obliterans was made in this case because of the long history, the observations at general examination, especially the involvement of the left arm with occlusion of the left radial and ulnar

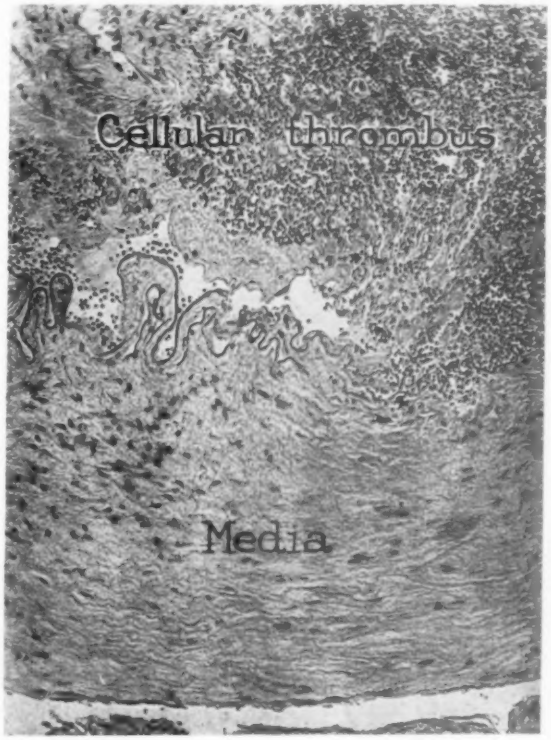

FIG. 2. A higher power of figure 1 showing more cellular detail and representing the rectangular area in figure 1 (hematoxylin and eosin stain x150).

arteries, the history of chronic, relapsing superficial phlebitis, and the later course of the disease. Occlusion of vessels of the hand is common in cases of thrombo-angiitis obliterans but is extremely rare in arteriosclerosis. Many patients with thrombo-angiitis obliterans with ulcers and trophic lesions could probably avoid amputation of the involved extremity, if they were willing to endure pain as this patient did. In many of our cases amputation is done because of pain rather than because of the extent of the gangrene or of the trophic changes.

Case 2. A man, aged sixty-five years, registered at The Mayo Clinic October 23, 1929. He complained chiefly of intermittent pain in the legs, and hemoptysis. He had smoked an average of seven small cigars daily since the age of twenty. For the last thirty years he had had arch fatigue and pain of the intermittent claudication type, and had worn many arch supports without relief. For the last fifteen years he had had mild intermittent claudication in the calves. At the time of admission he could walk only two city blocks without this pain. Rest for a few minutes always gave prompt relief. During the last year he had complained of cold feet, and observed that they were bluish-red when in the dependent position. For the last four months he had intermittent rest pain in the first and second left toes. Seven

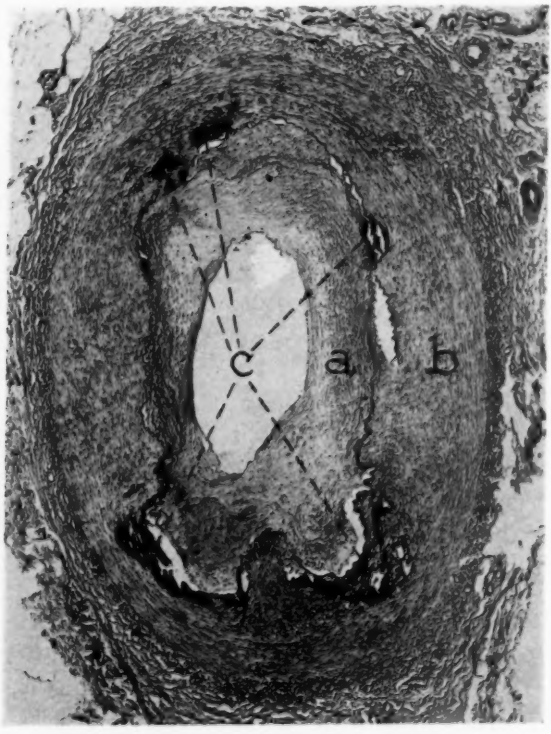

FIG. 3. Cross section of the posterior tibial artery from a subject with arteriosclerosis. Deposits of calcium salts (c) are present in the media (b). The intima (a) is thickened and is comparatively acellular (hematoxylin and eosin stain x35).

months prior to admission productive cough frequently with blood-tinged sputum developed following a "cold". On a few occasions he had coughed up 30 c.c. or more of bright red blood. There was no definite history of superficial phlebitis.

The patient appeared to be moderately well nourished, was approximately 5½ feet in height, and weighed 130 pounds. The thorax was barrel-shaped, with definite limitation in expansion. Râles were not present either before or after expiratory cough. Roentgenograms of the thorax showed ancient healed tuberculosis at the right apex. Examination of the sputum was negative for the bacillus of tuberculosis. The possibility of hemoptysis from a small area of bronchiectasis was considered. The heart showed compensatory cardiac hypertrophy, graded 1. The systolic blood pressure on admission was 175 and the diastolic 90, in millimeters of mercury. While the patient was under observation in the hospital the systolic pressure was 130 and the diastolic 60. All of the palpable vessels in the upper extremities pulsated normally. Both femoral arteries pulsated normally, and slight pulsation could be felt in the right popliteal artery, but pulsations could not be felt in the left popliteal artery or in the arteries of the feet. The arches in both feet appeared normal. With elevation of the feet, there was moderate blanching of the toes of the left foot. With the feet in the dependent position there was rubor, graded 1, of the toes of the right foot, graded 2, of the left foot, and moderate cyanosis of the second left toe. Examinations of the urine were negative. The con-

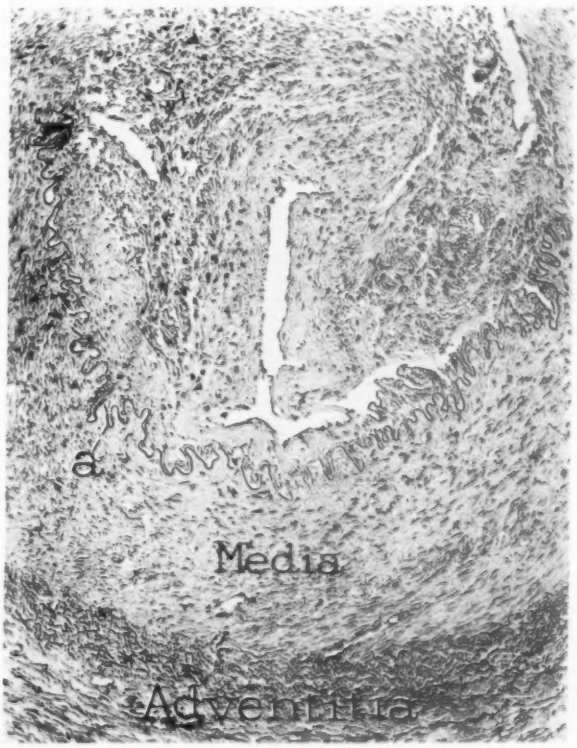

FIG. 4. Cross section of the dorsalis pedis artery. The lumen is occluded by a partially organized thrombus, which has been partially canalized. There is absence of calcification in the wall of the vessel. The internal elastic membrane (a) appears normal (hematoxylin and eosin stain x80).

centration of hemoglobin was 17.6 gm. in 100 c.c., and the leukocytes numbered 9,100 per cubic millimeter. The concentration of blood urea was 34 mg. in 100 c.c., and the blood sugar was 90 and 78 mg. The electrocardiogram was essentially negative. The return of phenolsulphonphthalein was 50 per cent in two hours. Roentgenograms of the feet and legs were negative for calcified vessels and for lesions of bone.

Radiant heat was applied to the legs for five to eight hours a day, and postural exercises were carried out three times daily. Intramuscular injections of typhoid vaccine were also given. The patient was instructed to restrict physical activity to the point of not producing pain in the lower extremities. Because of the thirty-year history of intermittent claudication (arterial closure), the slow onset of the disease, and the favorable response to treatment, we believed that the prognosis was fairly good for preservation of the extremities. However, a letter from the patient dated March 24, 1931, stated that during the past six months the left leg had been amputated (apparently below the knee). The stump did not heal and a second amputation above the knee was necessary.

The long history of occlusive vascular disease beginning at the age of thirty-five years, and the absence in the roentgenogram of evidence of calcification of the vessels make the diagnosis of thrombo-angiitis obliterans reasonably certain. The early use of arch supports is also suggestive. This history is the longest of this disease which is on record at The Mayo Clinic.

FIG. 5. Cross section of a deep vein of the left leg. The lumen is occluded by an ancient thrombus which has been canalized (Weigert's elastic tissue stain x40).

Case 3. A man, aged seventy-three years, was under observation at The Mayo Clinic in April, 1907, November, 1915, and March, 1929. Symptoms referable to the hands and feet were first observed in 1903. These consisted of the three-phase color reaction, white, red and blue, when the hands were exposed to cold. In 1906 the fifth right toe was amputated elsewhere for an unhealed ulcer. At the time of his first admission in 1907 he had an unhealed ulcer on the right great toe. The toe was amputated. During the next five or six years two or three similar ulcers developed which required from six to eight months to heal. At admission in 1915, there were ulcers on the second right and the first and fifth left toes, which had been present for approximately ten months.

Both feet appeared hyperemic in the dependent position. The general examination was otherwise essentially negative. The systolic blood pressure was 126 and the diastolic 86. Examinations of the urine were entirely negative. The concentration of hemoglobin was 89 per cent and the leukocytes numbered 10,800. The Wassermann reaction of the blood was negative. A roentgenogram of the thorax was negative, except for slight enlargement of the heart, graded 1. Roentgenograms of the feet were negative. It was believed at this time that the ulcers were due to obliterative arterial disease, but record was not made regarding pulsations in the arteries of the feet. However, rest, with the feet in a horizontal position, was advised until adequate collateral circulation was established.

During 1918 and 1919 the second right and the third left toes were amputated elsewhere for unhealed ulcers. It required from two to twelve months for these amputation wounds to heal. During the course of the patient's illness, he had approximately twelve ulcers on the tips of the toes. Fourteen

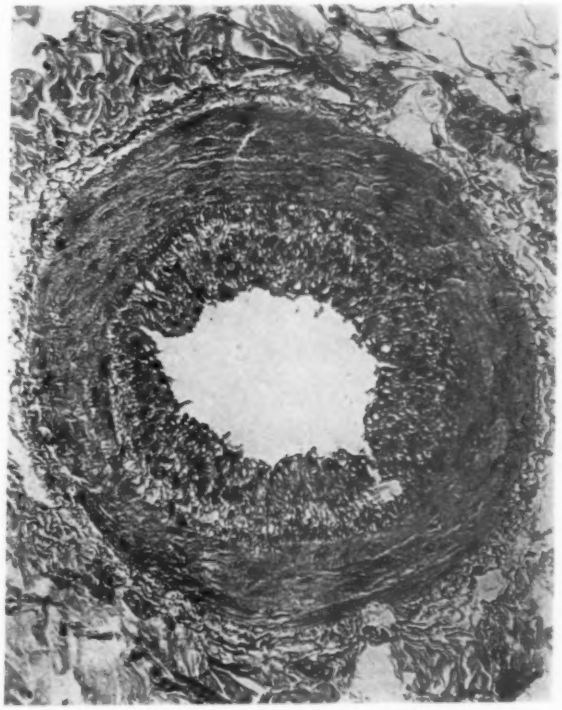

FIG. 6. Cross section of a small artery. Cellular thickening of the intima is shown (hematoxylin and eosin stain x135).

months prior to his third admission, March 6, 1929, an ulcer developed at the base of the left great toe, which gradually increased to about 2 cm. in diameter. There was little pain associated with these ulcers. For a period of twenty years, he had noticed an occasional small nodule beneath the skin. Whether these represented areas of superficial phlebitis could not be determined from the history. There was no definite history of intermittent claudication, although for a period of more than twenty years he did very little walking, and always took the best of care of his feet and legs. He had smoked an average of three cigars daily for the last fifty years, and had taken about three drinks of whiskey daily for approximately the same period.

Examination was essentially negative, except for the condition of the extremities. The patient seemed well preserved for his age. He was about 6 feet 2 inches in height, and weighed approximately 150 pounds. The systolic blood pressure was 120 and the diastolic 76. Both radial arteries pulsated normally but pulsations could not be felt in the ulnar arteries. Both femoral arteries pulsated normally. The pulsations in the right popliteal artery were reduced 50 per cent and pulsation could not be felt in the right dorsalis pedis or posterior tibial arteries. Pulsations could not be felt in the left popliteal, left dorsalis pedis and left posterior tibial arteries. The sclerosis in the peripheral arteries was graded 1. Examination of the urine was negative, except for a slight trace of albumin. The hemoglobin was 12.9 gm. in each 100 c.c. by the acid-hematin method. The erythrocytes numbered 4,380,000 and the leukocytes, 9,300. The differential count showed lymphocytes 13, large mononuclear cells 2, transitional cells 7, and

FIG. 7. Cross section of a small arteriole. Marked cellular thickening of the intima is shown, which almost completely occludes the lumen (hematoxylin and eosin stain x200).

neutrophils 78 per cent. The concentration of urea was 35 mg. in 100 c.c. of blood, uric acid was 2.76 mg. and sugar was 76 mg. Roentgenograms of the feet and legs were negative. The return of phenolsulphonphthalein was 40 per cent in two hours. The electrocardiographic report showed a rate of 86, auricular premature contractions, and aberrant QRS complex in derivations I and II, notched left ventricular preponderance, notched P wave in derivations I and II and inverted T wave in derivation III.

The ulcer at the base of the left great toe gradually increased in size and on the fourth

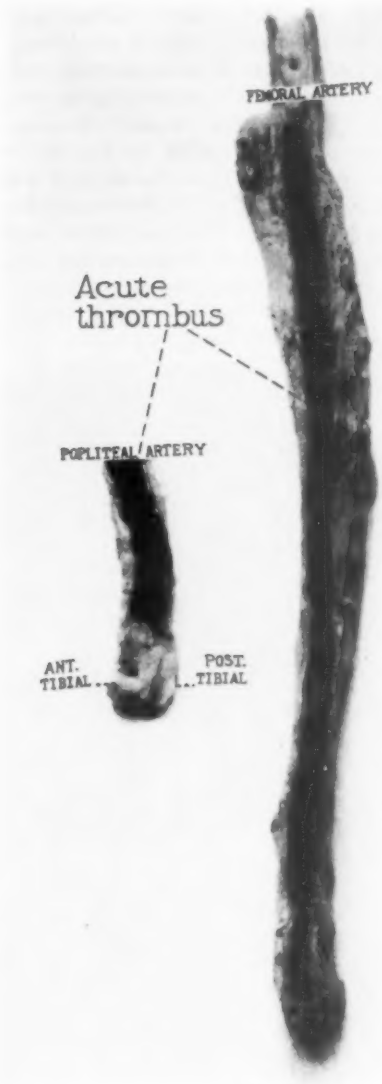

FIG. 8. Longitudinal sections of the left femoral and popliteal arteries showing the vessels occluded with an acute thrombus.

day after admission the dorsum of the foot became gangrenous. There was also a distinct change in the patient's general condition. The left leg was amputated March 11, 1930, at the juncture of the upper and middle third of the femur. The femoral artery was thrombosed at the site of the amputation. The afternoon of the operation, abdominal distention developed, which could not be relieved either by gastric or colonic lavage. The distention and toxemia increased, the blood urea rose to 130 mg. in 100 c.c. the following day, the patient's strength gradually failed, and he died forty-eight hours later, in spite of supportive measures.

At the bifurcation of the popliteal artery of the amputated leg, the vessel was occluded by an ancient and completely organized thrombus, about 1 cm. in length. The remainder of the popliteal artery was occluded by a recent red, partially organized thrombus. The posterior tibial artery was patent to the lower third of the leg. Below this level it was occluded by a partially organized thrombus (figures 1 and 2). Figures 1 and 2 should be compared with figure 3 which is the cross section of the posterior tibial artery of a subject with arteriosclerosis. The anterior tibial and dorsalis pedis arteries were occluded (figure 4) with an ancient organized thrombus. The deep veins were also involved in a similar occlusive process (figure 5). Many of the smaller arteries and arterioles showed active proliferation of intima (figures 6 and 7). At necropsy the left stump did not show evidence of infection, but the skin adjacent to the wound was dark red, indicating a poor blood supply. The left femoral artery (figure 8) was occluded with a recent red thrombus which extended up to Poupart's ligament. The iliac arteries were patent and did not show gross

FIG. 9. Cross section of the left external iliac artery. Thickening of the intima is shown (hematoxylin and eosin stain x150).

evidence of arteriosclerosis but it was shown to be present on microscopic examination (figure 9). The aorta was also patent and showed arteriosclerosis, graded 3 in the arch and upper thoracic portion, and graded 1 to 2 in the abdominal portion. In the abdominal aorta there was an area 3 by 3 cm. which was covered with relatively soft necrotic material; it is possible that an embolus may have broken off and lodged in the left popliteal artery, serving as the basis for the propagating thrombus which had completely filled the left popliteal and left femoral arteries. Other significant observations were not made at post mortem examination, except the presence of chronic mitral endocarditis, chronic duodenal ulcer, and mild atrophy of the brain with arteriosclerosis, graded 3, of the arteries composing the circle of Willis. Peritonitis was not present. The heart weighed 429 gm. and the coronary arteries showed arteriosclerotic changes, graded 2. The lungs showed evidence of congestion, but pneumonia was not present, either on gross or microscopic examination.

The long history (1903 to 1929) of symptoms in both hands and both feet, the occlusion of both ulnar arteries, the amputation of four toes at irregular intervals and the prolonged healing following, the absence of demonstrable calcification in the vessels by roentgen ray, and the appearance of the microscopic sections from the amputated leg, make the diagnosis of thrombo-angiitis obliterans certain. The arteriosclerosis in this case was not more advanced than would be expected among men of that age; in fact, it was not as advanced as we have often noted in younger persons who were having few, if any, symptoms referable to the extremities. The extent of the acute thrombosis in the left femoral artery (the thrombus extended from the bifurcation of the popliteal to Poupart's ligament) makes it doubtful whether the stump would have healed owing to the marked and sudden diminution in the blood supply to the extremity.

This case calls attention to the fact that age, of itself, does not eliminate thrombo-angiitis obliterans. The pathologic changes in the vessels of the amputated leg indicated the presence of chronic inflammatory rather than a degenerative type of disease and proved the diagnosis of thrombo-angiitis obliterans. No doubt an erroneous diagnosis of Raynaud's disease was made at the onset of symptoms, because of the color changes in the hands on exposure to cold. It should be emphasized again that the three-phase color reaction in men, when the hands and feet are exposed to cold, does not necessarily indicate Raynaud's disease; it usually indicates an early symptom of thrombo-angiitis obliterans. For a period of years, there had been a succession of digital ulcers, and gangrene, with amputation and slow healing. At the patient's subsequent visits to the clinic in 1907 and 1915, the correct diagnosis was not made.

Comment

Three cases of thrombo-angiitis obliterans in persons aged sixty-three, sixty-five and seventy-three years, respectively, are reported. One patient gave clinical evidence of having had the disease for more than twenty-six years, and another for more than thirty years.

A pathologically proved diagnosis was obtained in one case. One patient, a man aged seventy-three years, is the oldest subject we have seen with this disease, and so far as we are aware is the oldest on record.

The data concerning these patients give additional light on prognosis. The disease is characterized by a chronic relapsing lesion of the vessels, and occlusion and collateral circulation struggle for supremacy. The element of time is most important in this struggle, since on this, preservation of the part rests. If the intervals between relapses are short, and the time for adequate collateral circulation is brief, trophic changes and gangrene are likely to ensue. Conversely, if the intervals of time between relapses are long, collateral circulation becomes adequate and sufficient supply of blood to the distal areas is assured. The first consideration regarding prognosis is the frequency of the exacerbation of the disease. Our experience in a large number of cases of thrombo-angiitis obliterans shows clearly that a high percentage of bad prognoses (regarding amputation) is not justified in this disease. Probably 20 to 30 per cent of patients will lose one or more limbs. An increasing number of early diagnoses, the institution of protective and therapeutic measures, and the institution of protective types of operation, as sympathetic ganglionectomy in selected cases, are still further reducing this percentage. Increasing knowledge by the profession of the dangers of surgical tinkering with the affected digits in which the supply of blood is already diminished will perhaps accomplish greater changes in the prognosis than any other single factor.

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Treatment of Angina Pectoris With a Tissue Vasodilator Extract–Preliminary Report*†

By Joseph B. Wolffe, M.D., Donald Findlay, Ph.D., and Edward Dessen, M.D., *Philadelphia, Pa.*

In 1926 E. K. Frey and H. Kraut[1] found a substance in the urine which they demonstrated to have vasodilator properties, and which they believed to be a circulation hormone (Kreislaufhormon). In 1929 Frey[2] operated on a patient who had a pancreatic cyst and found that the cystic fluid was rich in this particular hormone. They have since studied this product extensively and have come to the following conclusions:

1. The hormone is present in the blood and is excreted in the urine.
2. The hormone is present in the blood mainly in an inactivated form and excreted in the urine in its active state.
3. The active hormone obtained from the urine can be rendered inert by the addition of blood serum.
4. The inactivated hormone can be reactivated by the addition of acid or a certain vegetable enzyme, papain.
5. The hormone is not histamine.
6. The hormone is elaborated and stored mainly in the pancreas.
7. The action of the hormone is to cause a drop in blood pressure by means of vasodilation.
8. The hormone can be used to advantage in patients suffering from angiospastic diseases, coronary sclerosis, and certain forms of hypertension.

At the session of the Berliner Medizinische Gesellschaft, July 9, 1930, Frey[3] discussed this newly discovered internal secretion and also reported the isolation and purification of a substance, a polypeptide, which inactivates it. "The relation of the link between the hormone and the inactivator is dependent upon the prevailing reaction in the tissues, so that a slight shifting towards the acid side produced by the appearance of acid metabolism releases the link between the hormone and the inactivator, whereby the vasodilator action comes into operation." In this alternation between union and releasing of the active substance—which is brought about by a slight change of the hydrogen ion concentration—Frey sees its real physiologic importance which in connection with internal secretion proves the substance to be a genuine hormone. He also reported the successful use of the hormone for the past two years. "The blood pressure in essential hypertension not caused by the kidneys drops considerably and remains at a lower level after the injections are discontinued. In

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angina pectoris and especially in intermittent claudication the attacks subside. Amputations that in necrosis and gangrene of the extremities would otherwise have been necessary, were avoided, owing to the action of the remedy."

P. Gley and N. Kisthinios[4], in 1929, prepared a substance from the pancreas which is apparently the same as the one described by Frey and Kraut. They found that the extract had vasodilator properties, was free of insulin in the animal under experimentation, antagonized the action of epinephrine, and caused a transitory hypotension that was not due to choline, histamine, or peptones. H. Vaquez, R. Giroux and N. Kisthinios[5] have used the product clinically in the treatment of angina pectoris and have reported the most remarkable results. They treated twenty patients in various stages of angina, and in practically every case succeeded in obtaining almost complete symptomatic relief.

Recently J. S. Schwartzman[6] reported the results of using a voluntary muscle extract in cases of angina pectoris. He explains the favorable effects that he obtained by the presence in the muscle extract of a substance that acts as an antispasmodic, the substance being liberated in a muscle during exercise. M. S. Schwartzman[7] used the preparation in cases of angina pectoris and also reports very gratifying results. In reference to the antispasmodic substance being found in voluntary muscle only, K. Fahrenkamp and H. Schneider[8] this past year made a comparative study on man of two extracts, one from skeletal muscle, the other from heart muscle; this latter was previously believed by Haberlandt to represent a true heart hormone. They found that the effects of the two were identical. Administered either orally or intravenously each of these extracts completely controlled attacks of angina pectoris. The authors concluded that the heart muscle extract does not represent a true heart hormone.

These findings add significance to the work of A. M. Drury and A. Szent Gyorgi[9]. They studied the effect on the heart of simple extracts of heart muscle, and of other body tissues. Some of their conclusions were as follows:

1. Simple extracts of heart muscle, brain, kidney and spleen have a definite and transient effect upon the mammalian heart.
2. The substance responsible for this action has been isolated and appears from its chemical properties to be adenylic acid. Its activity apparently depends upon the ease with which the substance is deaminated in the body.
3. Adenosine, prepared from yeast nucleic acid, had an action identical to adenylic acid.
4. The physiological activity of both substances has been tested by intravenous injection into the whole animal.
5. Among other effects upon the heart, they slow the rate, impair conduction from auricle to ventricle and arrest experimentally produced auricular fibrilation; they shorten the absolute refractory period of an improved slowed conduction in the auricle due to high rates of beating.
6. They lower general arterial pressure. This is due in part to the cardiac slowing and in part

to a general arterial dilatation. They dilate the coronary vessels and inhibit intestinal movements.

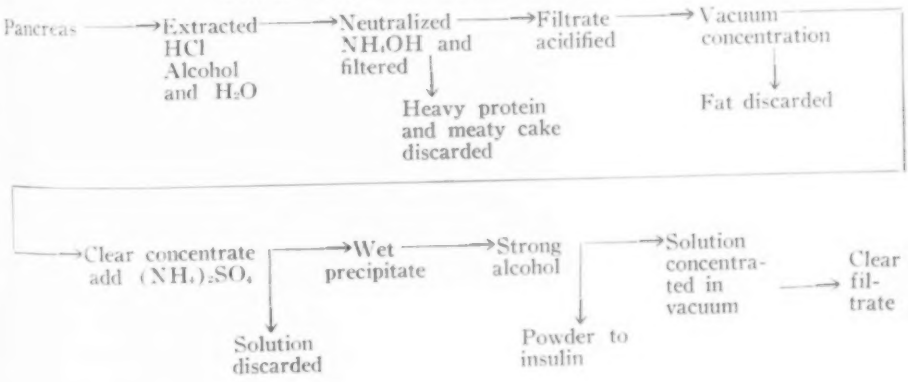
We believe that all these substances mentioned are identical, as borne out by our studies, and we are at present making further investigations to prove this.

After considering all the experimental and clinical data on the subject, as well as our own work, it seems to us that we are dealing here with an active principle that is either adenylic acid or adenosine. In this connection we want to take cognizance of the editorial in the Journal of the American Medical Association of October 11, 1930. The editor there inclines to the belief that the so-called heart hormone can be obtained in any body tissue and is most likely histamine. While we do not believe that the substance in question is a specific heart hormone, and although it is true that it can be obtained from various body tissues, it nevertheless has definite primary vasodilator properties. It is not histamine as the editor infers. Of this we are quite certain.

We became interested in this product since it is an adjunct in the treatment of angina pectoris and other vascular diseases. We prepared an extract in a manner similar to the method of P. Gley and N. Kisthinios[10]. The ground pancreas was extracted with a menstruum of alcohol and water, so that the final alcoholometer reading was 63 per cent. Sufficient hydrochloric acid was used to yield a pH of 2.4. This mixture was run through a colloid mill for thorough extraction. The product was neutralized with ammonia and filtered. This filtrate, acidified with sulphuric acid, was concentrated under vacuum and the clear concentrate sulphated, using ammonium sulphate to one-half saturation. The wet precipitate treated with strong alcohol yielded a powder containing insulin and a 90 per cent alcoholic liquor. This liquor contained alcoholic extractions of the precipitate and the mother liquor wetting it. It was concentrated with the addition of water.

The clear filtrate obtained in the above manner was used for purposes of injection. In making a preparation for oral administration at stage eight, instead of sulphating and collecting the insulin, the product was alcoholized to ninety per cent and then concentrated.

FIG. 1. Diagram of method of preparation.



We then corroborated the findings that it caused a primary drop in arterial pressure when injected intravenously, antagonized the action of adrenalin and slowed the cardiac rate. This is seen in the following figures.

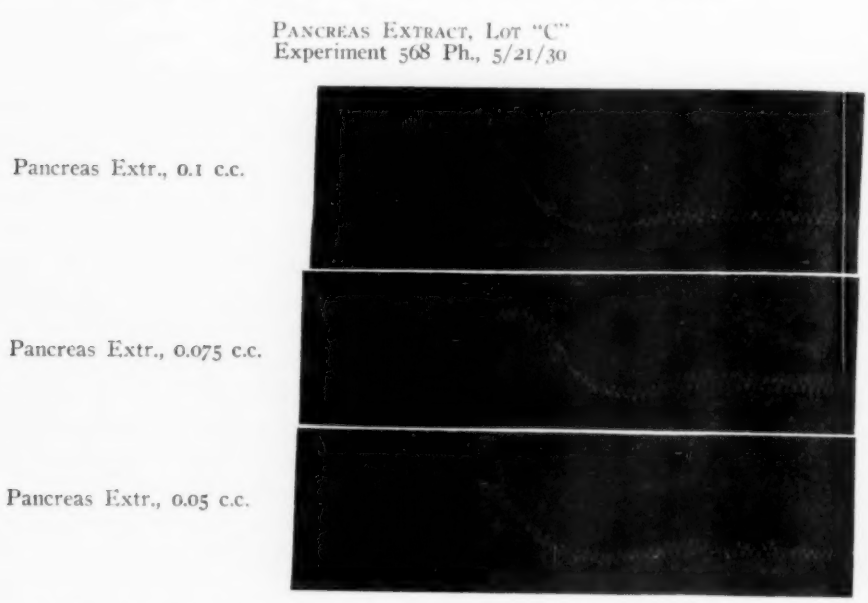


Fig. 2.—Drop in arterial tension following intravenous injection of vasodilator extract.

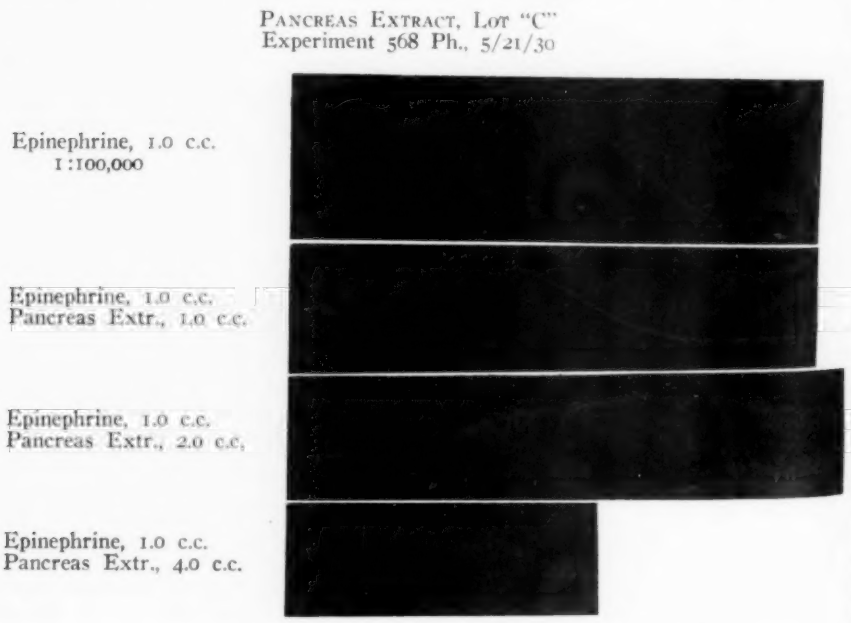


Fig. 3.—Antagonization of adrenalin effect by vasodilator extract.

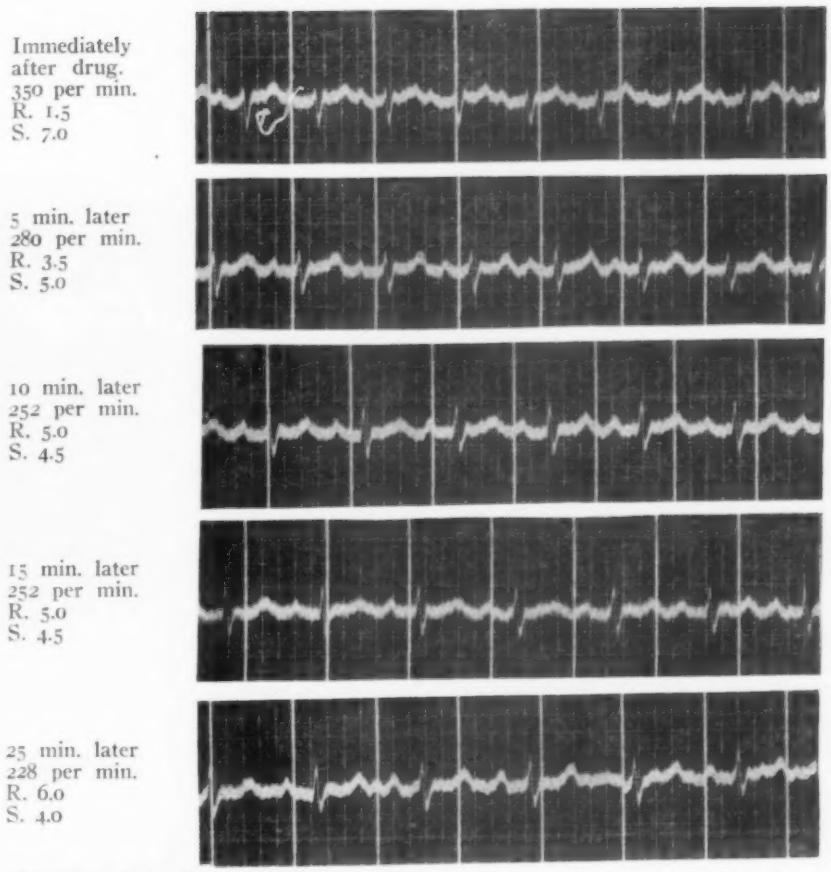


FIG. 4. Electrocardiographic tracing of rooster, showing cardiac slowing following injection of vasodilator extract.

In order to make sure that the ammonium sulphate used in the process had no hypotensive effect, we administered 0.1 c.c. of 5 per cent ammonium sulphate. No drop in tension followed.

To rule out the possibility that insulin was responsible for the pharmacologic effect, an injection of .075 c.c. of insulin (20 units) was given. This also failed to cause any appreciable change in blood pressure. To make certain that the animal was still responding, the experiment was concluded with another injection of the vasodilator extract. The result was similar to the first response, a drop in tension occurring.

We then proceeded to use this vasodilator extract by intramuscular injection.

PREPARATION USED

The extract* which we used, prepared in the above described manner contained 15 hypotensive units per c.c. A hypotensive unit according to the method of standardization of P. Gley and N. Kisthinios[10] is that amount of the extract which when suddenly in-

*We are indebted to Sharpe & Dohme, Inc., for their kindness and cooperation in the preparation of the extract.

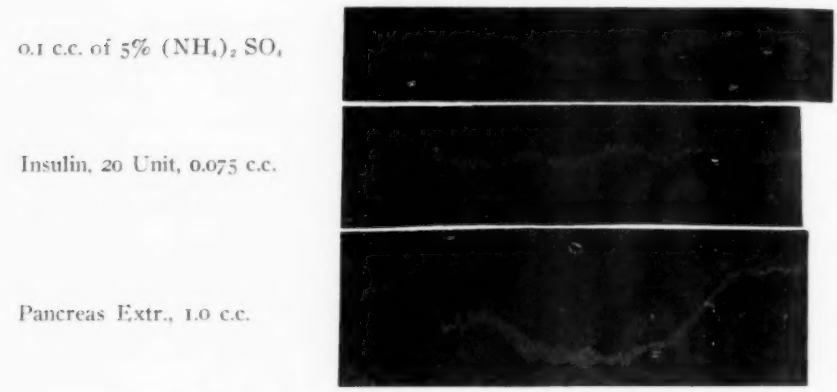


Fig. 5.—Comparative effect of recording arterial pressure of injections of $(NH_4)_2 SO_4$ insulin and vasodilator extract.

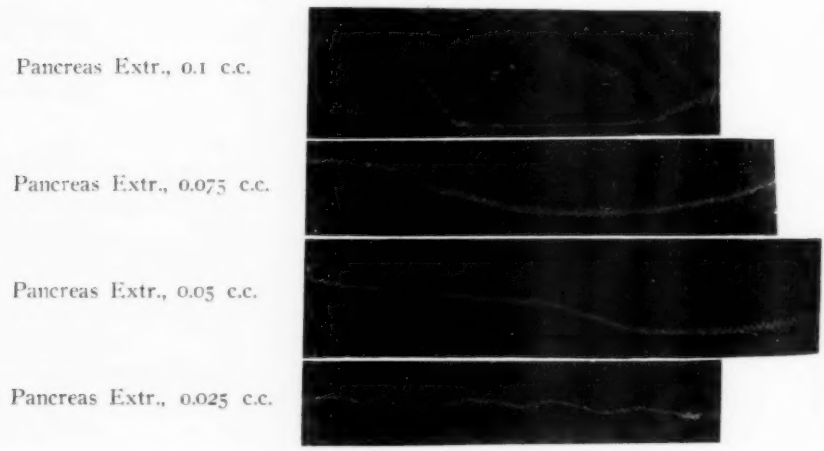

Pancreas Extract, Lot "C 2"
Experiment 568 Ph., 5/28/30
Pancreas Extr., 0.1 c.c.
Pancreas Extr., 0.075 c.c.
Pancreas Extr., 0.05 c.c.
Pancreas Extr., 0.025 c.c.

Fig. 6.—Standardization of vasodilator extract.

jected into the jugular vein of a rabbit weighing two kilograms produced a drop in arterial tension just appreciable on the tracing.

The experiments that we conducted to determine the toxicity of the extract as indicated in the tables below show it to be nontoxic.

TABLE 1

DETERMINATION OF TOXICITY OF VASODILATOR EXTRACT

No. of Rabbit	Weight Grams	Days	Drug	Kilo Dose	Remarks
5927	2100	0	Vasodilator Extract Intravenously	10 c.c. per kilo.	Normal
	1900	1			Normal
	1880	2			Normal
	1800	3			Normal
	1910	6			Normal
	1870	8			Normal
	1890	9			Normal
	1840	10			Normal
	1940	12			Normal
	1960	15			Normal
	2000	16			Normal
	2090	21			Normal
	Out†				
5934	1600	0	Vasodilator Extract Intravenously	20 c.c. per kilo.	Normal
	1590	1			Normal
	1620	3			Normal
	1670	6			Normal
	1690	7			Normal
	1720	12			Normal
	1740	16			
	Out†				
5936	1910	0	Vasodilator Extract Intravenously	30 c.c. per kilo.	Animal had slight convulsions; was depressed and shaking; breathed heavily and was weak.
	1780	1			Normal
	1750	3			Normal
	1830	4			Normal
	1870	5			Normal
	1850	10			Normal
	1890	14			Normal
	Out†				
5937	1900	0	Vasodilator Extract Intravenously	15 c.c. per kilo.	Animal had convulsions; prostrated for 15 min. Later the breathing was heavy and it recovered slightly. 30 min. later recovered almost completely.
	1860	1			Normal
	1840	3			Normal
	1890	4			Normal
	1930	5			Normal
	2010	10			Normal
	2080	14			Normal
	Out†				

†Indicates that the animal was discarded after 2 or more weeks of observation.

No. of Rabbit	Weight Grams	Days	Drug	Kilo Dose	Remarks
5948	1900	0	Vasodilator Extract Intravenously	25 c.c. per kilo.	Slight convulsions; recovered after 3 minutes, but was very weak for 30 minutes.
	1740	1			Normal
	1730	2			Normal
	1790	5			Normal
	1840	6	Rec'd 15 c.c. glucose 10%. 5 minutes before extract.		Normal
	1850	7			Normal
	1840	8			Normal
	1860	10			Normal
	1810	12			Normal
5950	2010	0	Vasodilator Extract Intravenously	1.25 c.c. per kilo.	No reaction
	2090	1			Normal
	2110	2			Normal
	2160	5	20 c.c. concentrated down to 2.5 c.c.		Normal
	2170	6			Normal
	2190	7			Normal
	2220	8	Animal rec'd 15 c.c. of 10% glucose intravenously 5 min. before extract.		Normal
	2250	10			Normal
	2210	12			Normal

Our investigation as to the possibility of an anaphylactic action due to any protein that the substance might contain, also gave negative results.

Selection of Clinical Cases

The cases selected for trial for the most part had suffered from angina pectoris for a number of years and had in the main resisted all forms of treatment. Nitroglycerin afforded a few of them relief during an attack but in no way influenced the recurrences. The patients were from the Temple University Hospital, Willow Crest Convalescent Home, and our own private practice. Twenty cases were studied. All administrations and observations were under our own personal supervision. Subjects who had experienced a recent coronary occlusion were rejected. Electrocardiograms and teleroentgenograms were obtained in every case. The whole series had negative blood Wassermanns and negligible urinary findings. Blood pressures were normal in 8 cases and elevated in 12. Cardiac enlargement was present in 14 cases and electrocardiograms showed inverted waves suggestive of supposed coronary disease in 7 cases. Two showed coronary waves during an attack, and two others who had normal electrocardiograms at the beginning of the treatment developed so-called coronary waves dur-

TABLE II
TEST FOR ANAPHYLACTIC REACTION

No. of Guinea Pig	Gram Weight	Days	Drug	Amount	Remarks
1	390	0	Sterile horse serum 1:1,000 made of 1 c.c. undiluted horse serum plus 99.9 c.c. salt solution.	1 c.c. 1:1000 solution	10:50 A. M.
		11	Intraperitoneally	1 c.c. of undiluted serum	10:53 A. M. animal restless and squealing 11:00 A. M. scratching mouth with paws 11:45 A. M. appeared normal
2	310	0	Sterile horse serum Intraperitoneally	1 c.c. 1:1000 solution	Injected 11:25 A. M.
		11	Intraperitoneally	1 c.c. undiluted serum.	11:28 animal had chills, became restless and squealed 12:00 animal appeared normal
3	350	0	Vasodilator extract 1:1000 Intraperitoneally	1 c.c.	Injected 1:49 P. M.
		11	Intraperitoneally	10 c.c. undiluted pancreas extract	No reaction: the animal remained quiet during many hours of observation

ing the time they were receiving the injections. Four of the group had an increased blood pressure during an attack. Three of the patients with a normal pressure at the time of the study were known to have had hypertension at some previous time.

METHOD OF TREATMENT

The method of treatment consisted of daily intramuscular injections, the dosage varying from a minimum of 60 units (4 c.c) to a maximum of 150 units (10 c.c.). The usual dose was 75 units. Where treatment was temporarily stopped the interval before resumption was never more than a week. Every case had been receiving theobromine sodium salicylate, grs. 5; acetylsalicylic acid, grs. 5, and phenobarbital, grs. ¼, before the injections were started, with some slight favorable effect. This medication was not discontinued when the vasodilator extract therapy was begun. A dose of oleum ricini, 2 oz., was given once every two weeks. Smoking in any form was absolutely forbidden. Instructions were given as to diet and time of meals to avoid any discomfort incident to flatulence. Care was taken to have the patients avoid over-exertion or over-excitement; in other words, we were particular to safeguard against apparently minor disturbing influences.

RESULTS

There was a cessation of the anginal attacks in 11 of the 20 cases. Six others experienced some relief, but

TABLE III
TABLE OF CASES

Cases	History of Attacks	Hypertension			Cardiac Enlargement	Evidence of Organic Aortic Change		Effect of Nitroglycerin	Amount of Extract Used Units	Results	Remarks
		During Observation	During An Attack	Previous History		Roentgen	Clinical				
I	2 yr. 7 mo.	0	0	+	0	+	+	Occasional relief	3000	Free of pain	
II	10 mo.	0	0	+	+	+	+	Occasional relief	1620	No relief	Died of coronary thrombosis; decompensated during treatment.
III	2 yr.	+	0	0	+	+	+	Not used	2160	Free of pain	Able to go about usual duties.
IV	1 yr. 6 mo.	0	0	0	0	0	0	Not used	2000	Partially relieved	Findings mainly subjective.
V	3 yr. 6 mo.	+	+	0	0	+	+	Gave relief	1620	Free of pain	Been taking extract by mouth since.
VI	1 yr. 6 mo.	+	0	0	+	+	+	Not used	1620	Partially relieved	Decompensated during treatment.
VII	2 yr.	0	+	0	+	+	0	Not used	2160	Free of pain	Been taking extract by mouth since.
VIII	2 yr. 6 mo.	0	0	?	+	+	+	Not used	2400	No relief	Died of coronary attack during coitus. Decompensated during treatment.
IX	4 yr.	+	+	0	+	+	0	Occasional relief	2700	Free of pain	Died 6 mo. after discharge, of coronary thrombosis.
X	2 mo.	0	0	+	+	+	0	Not used	720	Partially relieved	Auricular fibrillation; refused to continue treatment.

XI	5 mo.	0	0	0	0	0	0	Not used	2160	Free of pain	Also relieved of intermittent claudication, for which sympathectomy had been advised, but not performed.
XII	2 yr.	0	0	0	0	+	+	Not used	2160	Free of pain	Attacks ceased and then recurred during treatment, then ceased again.
XIII	1 yr. 10 mo.	+	0	0	+	+	0	Gave relief	1600	Partially relieved	
XIV	4 mo.	+	0	0	+	+	0	Not used	3600	Free of pain	Attacks continued until treatment was well advanced.
XV	2 yr.	+	0	0	+	+	0	Occasional relief	5000	Almost entirely relieved	Pain continued until 4 courses of injections were given.
XVI	4 mo.	+	0	0	+	+	0	Not used	3600	Free of pain	
XVII	3 yr.	+	0	0	+	+	+	Failed to relieve	2500	No relief	Stopped treatment, believed it made him worse.
XVIII	4 mo.	+	0	0	+	+	+	Gave relief	2000	Partially relieved	
XIX	1 yr. 6 mo.	+	0	0	+—	+	+	Gave relief	5000	Free of pain	Most stubborn case of series; note number of units used.
XX	8 mo.	+	+	0	0	+	0	Not used	3000	Free of pain	Symptoms were epigastric.
Totals 20		12	4	3	13 (1?)	18	10	4 relieved		11 relieved 6 partially relieved 3 not relieved	

still complained of occasional mild paroxysms. In 3 cases the result was a failure.

The following case history is illustrative of the group who were relieved of their anginal attacks.

Case 5. M. C., age 50, salesman. The patient was first seen in 1928. He complained of attacks of substernal pain radiating to the throat and left arm. The attacks were precipitated by excitement or exertion and lasted from three to ten minutes. They were occurring about once in two weeks. Although he complained of dyspnea after an attack he never suffered from any respiratory embarrassment at any other time. Upon physical examination we found his heart to be of normal size, the heart muscle tone somewhat muffled; the rhythm and rate were normal. There was a systolic roughening over the aortic area. Blood pressure 180 over 95.

The electrocardiogram revealed the QRS complexes to be of rather low amplitude (figure 7), but otherwise showed no abnormalities. The teleroentgenogram showed the cardiac silhouette to be normal, but the aortic arch was slightly widened and deflected upward and to the left.

The patient was given a combination of theobromine, acetylsalicylic acid, luminal, nitroglycerin, and codeine sulphate. He felt somewhat better but he had two severe attacks at the end of the month. He was then admitted to the hospital where he was given a course of Nauheim baths and injections of sodium citrate. He improved very much in the hospital and after his discharge he had only a few minor attacks until April, 1929. However, tracings taken at intervals showed progressive cardiac damage.

In April the patient suffered several severe attacks of angina and was again admitted to the hospital for a similar course of treatment. This time he felt fairly well until January, 1930. He then had several severe attacks and morphine had to be resorted to. Hitherto nitroglycerin had been effective in controlling the painful crises. The attacks now occurred several times daily. After a week of palliative measures without relief we commenced to give him injections of vasodilator extract, 60 units daily, for twelve

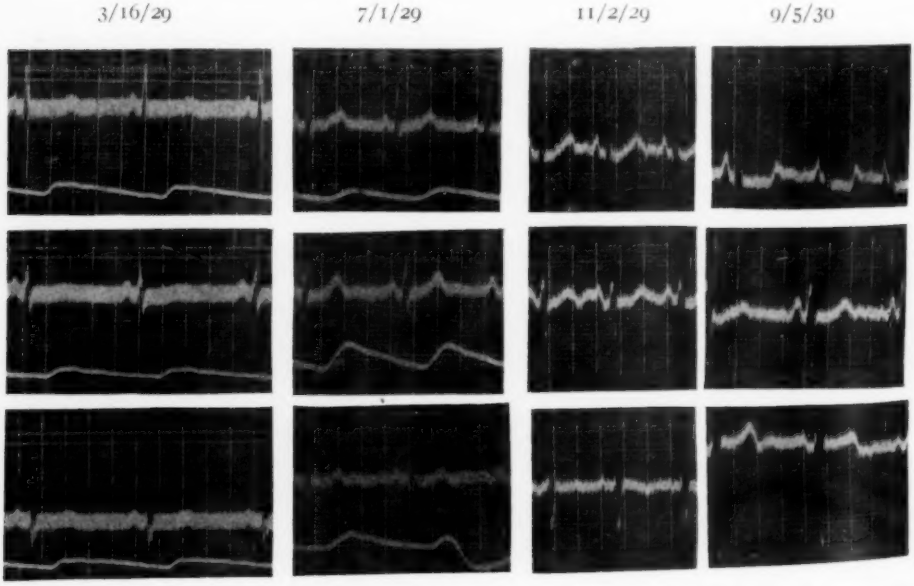


FIG. 7.—Electrocardiograph, Case V, showing evidence of progressive heart damage. Note the changes in the ventricular complexes.

days. He had no attacks while taking the injections. The following week he had a minor attack. We then gave him another series of injections, 75 units daily for twelve days. He has had no attacks to date. He received no more injections but he has taken 60 units by mouth daily since.

The following patient also responded very gratifyingly to the vasodilator extract.

Case 16, M. L., Age 51, machine operator. He had been suffering from the subjective symptoms of high blood pressure for three years. He was admitted to the hospital in September, 1929, for this condition. After being there but a few days he was seized with an attack of excruciating pain over the precordium which left him with a burning substernal sensation. He then claimed that he had occasionally experienced similar attacks but much milder in character for over a year. His blood pressure ranged between 157 to 200 systolic and 90 to 110 diastolic. Teleroentgenogram of the heart showed it to be generally hypertrophied with slight widening of the aorta. The patient was in the hospital for three months during which time he had several severe attacks and many minor ones. We began giving him the vasodilator extract by injection February 15, 1930, until he had received about 3600 units. He has been free from attacks since.

The next history is that of a patient with coronary occlusion whom we succeeded in relieving of her pain, but who died six months after we had ceased treating her.

Case 9, G. H., age 53, housewife. The patient first came under our observation in January, 1928, with a history of a few years' duration, of attacks of precordial pain radiating to both shoulders and to the left arm. She also complained of constant headaches and dizzy spells. Her blood pressure was 225 over 90. She was sent to the hospital. Her teleroentgenogram revealed the heart to be enlarged in its transverse diameter and the aorta to be widened. She felt better after a three months' stay in the hospital and a similar period of convalescense at a seaside resort. However, as soon as she returned to her home she began to have attacks. Two months later she was hospitalized again.

On March 1, 1930, she began to receive daily injections of the vasodilator extract. She received in all 2700 units and ceased to have even the slightest attacks. She felt so well that she failed to report for observation at appointed times. A short time ago we were called to see her and found her moribund from what appeared to be a coronary occlusion. A few days later she died.

The following is a case of the type that we grouped as being partially relieved.

Case 13, A. M., age 62, bookkeeper. The patient dated her illness to November, 1928, when she suddenly experienced a severe cramp in the epigastrium while walking. She was immediately rushed to the hospital where she was treated for acute indigestion. At this time it was discovered that she had hypertension and therefore she remained under medical supervision. When we saw her she complained also of a sensation of weakness around the heart, dyspnea, and palpitation, and, on excessive exertion, of occasional attacks of excruciating pain in the left shoulder, which would leave her very weak. These shoulder pains would be relieved by a hot water bag over the precordium or by drinking hot water. In February, 1930, we had her admitted to the hospital for treatment. Teleroentgenograms showed the heart to be enlarged in its transverse diameter, and the descending arch of the aorta to be prominent. Her blood pressure was 170 over 85.

Commencing February 3, 1930, she was given daily injections intramuscularly of vasodilator extract. She had one attack after the fourth injection which she claimed was the worst she ever had. As a matter of fact we had some difficulty in convincing her to continue with the injections. The attack was relieved by 1/100 gr. of nitroglycerin. She remained in the hospital for two months during which time she received a total of 1600 units. During this time she was receiving also theobromine, luminal, and acetylsalicylic acid, and a dose of castor oil every other week. We last heard of her

in September, 1930. She claimed that she had been subject to attacks of palpitation and cardiac discomfort, which according to her history seemed to be due to premature beats. She had suffered no definite anginal attacks. Physical examination revealed no change.

The course of events in one of the cases in which the result was a failure, was as follows:

Case 2, S. K., age 63, had not worked for four years due to poor health. The patient was first seen in December, 1929. He was suffering from severe attacks of precordial pain and a strangling sensation, with the radiation of the pain to both shoulders and arms. The patient was extremely ill with marked signs of congestive cardiac failure, and his skin was cold and clammy. He appeared to be much older than his stated age. His blood pressure was 120 over 80. He had been suffering from these attacks for the past eight months but in the last two months they had become progressively worse, until they were unbearable. His doctor had to resort to morphine for the last month in order to give him relief. He was removed to the hospital for six weeks and was given a course of Nauheim baths. The teleroentgenogram showed his heart to be enlarged in its transverse diameter and the aorta to be widened.

While in the hospital he did very well, requiring only one hypodermic of morphine during his stay. Until the time of discharge he felt better, but when he went home he commenced to have attacks again.

On February 3, 1930, he began to receive the injections of vasodilator extract, 1620 units in all. He had no relief during this time and soon developed congestive cardiac failure which could not be checked in spite of stimulation. Morphine had to be resorted to and he died of progressive cardiac failure.

Summary

Thus in 55 per cent of our cases we were able to obtain clinical relief by the use of the tissue extract for which we propose the name "antisympathone". Thirty per cent were partially relieved. Failure was met with in 15 per cent of the cases. Most patients developed "coronary" "T" waves at the same time that they improved symptomatically. (Figures 7 and 8). One patient who suffered from severe intermittent claudication in addition to angina and had been advised to have a sympathectomy performed for the former, was relieved of both complaints by antisympathone. The four patients who had a rise of blood pressure during an attack were all relieved. Two of the three patients who failed to respond were decompensated at the time treatment was administered. Hence they can be regarded as unfit for trial, since Vaquez also points out the certainty of failure if treatment is undertaken in such instances.

Comment

It is our belief that antisympathone is a valuable addition to the therapeutic armamentarium against angina pectoris. This dread syndrome has long stood invulnerable in very many instances to all methods of treatment. What occasional good results we have hitherto obtained that were more than merely temporary, could never be entirely ascribed to any one drug or therapy. The use of the vasodilator extract promises much better results. To say that it will permanently relieve every case of angina pectoris is to assert a belief that is not warranted by the character of our results or the time that they have endured. But to conclude that it will at least produce a remission in half of the cases is only a conservative estimate of what we have found. However, we do not believe that the vasodilator therapy removes

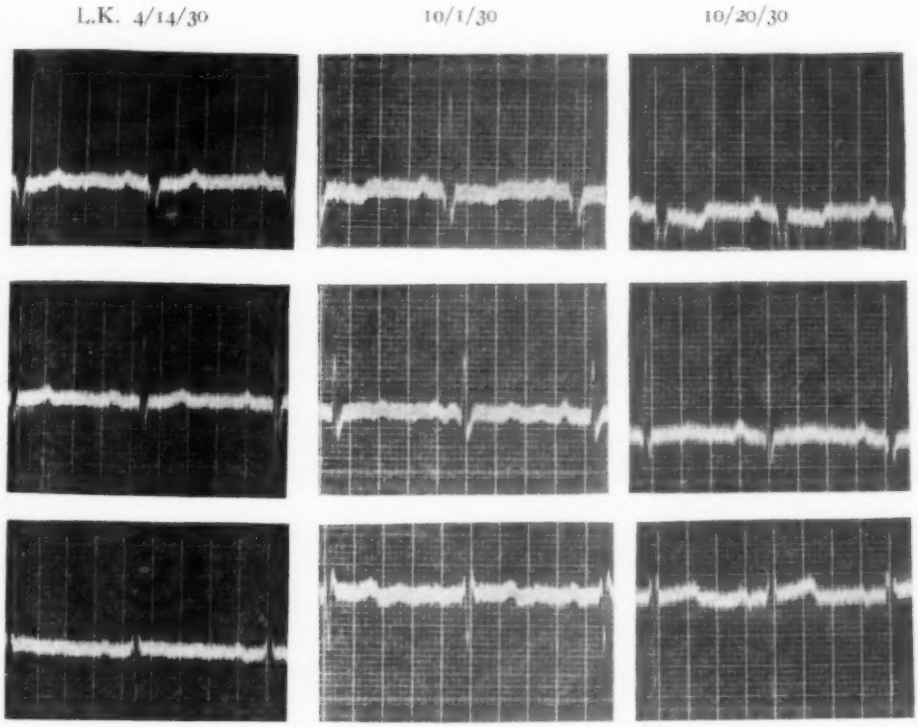


FIG. 8.—Electrocardiograph, Case XV, showing development of coronary T wave during treatment.

the lesions underlying the anginal attacks. As noted above, one of our patients completely freed of painful crises, experienced a coronary occlusion that was fatal; two others developed coronary "T" waves while under treatment (figures 7 and 8).

A few words at this time as to the modus operandi of the extract in relieving angina pectoris would not be amiss. It was the feeling of the French investigators that the beneficial results were due to a trophic action of the extract on the vascular system entirely separate from its hypotensive effects. Several of these patients had no hypertension to begin with and were benefited and several others continued to suffer although their tension was lowered. We have treated some patients suffering from obliterative arterial diseases of the extremities with this substance and observed improvement. Patients who suffered from intermittent claudication have been greatly benefited by the use of this extract.

Frey's opinion was that all therapeutic benefits derived from the use of the circulation hormone were attributable to its vasodilator action. He mentions good results which he obtained in various angiospastic diseases, coronary scleroses and hypertension. H. Schauder[11] recently reported the case of a patient who for more than a year had suffered from severe intermittent claudication and arteriosclerosis of the extremities which resisted all therapy.

Treated with Frey and Kraut's circulation hormone the symptoms disappeared almost completely and the good results have persisted for thirteen months.

The extract unquestionably has vasodilator properties. Work done on the dog leads us to believe that in this animal at least the primary fall in pressure is followed by a secondary rise. We are at present engaged in testing it on a large group of cases suffering from Buerger's disease and other forms of arterial disease, to determine its clinical applicability. However, it is our belief that the action of the vasodilator extract in relieving angina is associated with its adrenalin neutralizing properties. While the extent of our research on this score only permits us to speculate about it at this time, there are several thoughts that we would like to emphasize.

Sometime ago Levine, Ernstene, and Jacobson[12] showed that an anginal attack could be induced in almost every instance in patients suffering from angina pectoris by the subcutaneous injection of 1 c.c. of 1 to 1000 epinephrine solution. Control subjects did not experience that reaction.

Loewi[13] as far back as 1908, experimenting on animals, concluded that the pancreas through an internal secretion (now known to be insulin) furnished a chemical substance which is a depressor or inhibitor of the sympathetic nervous system. The effects of adrenalin, which is a sympathetic excitant, were antagonized or lost. Loewi tried to form a clinical test for pancreatic function from these conclusions, using the reaction of the iris to adrenalin as an index. The applicability and fate of this test which bears his name is not our concern at this time. The thought that we would like to bring out is that if adrenalin injected into certain patients subject to angina will produce an attack, and if a certain vasodilator obtained from the pancreas moderates the action of adrenalin, a possible explanation of the favorable action of pancreatic extract in relieving angina lies in this very neutralizing property. In other words, antisympathone acts in the same manner as a sympathectomy. However, some cases of angina pectoris seem to be associated with a preponderance of so-called parasympathetic influences on the heart and other viscera over sympathetic influences. In these cases the use of antisympathone must be strenuously avoided.

Of course Levine's work does not prove that anginal attacks as they occur in ordinary life are caused by an influx of adrenalin to the circulation. But the frequency of the paroxysms following effort, fright, et cetera, and the common, if not constant observation of the increase in blood pressure during an attack, could readily be explained by an increased adrenalin output in a patient with a damaged cardiovascular system. In fact, as we have just stated, in some cases of angina pectoris parasympathetic influences seem to be predominant.

Whether the injections of antisympathone stimulate further production of its active principle in the pancreas, or whether the extract acts as a buffer against adrenalin in direct proportion to the amount injected, and whether there is an associated pancreatic disease or deficiency in patients suffering from angina, are questions

that all may be properly asked at this point. Much work and research are necessary before they can be answered; and it is our hope that we have afforded some stimulus to thought and investigation in this direction.

Our purpose in bringing this product to the attention of the profession without any delay is to promote its wide clinical trial. Our work has been far from conclusive. The impossibility of the expression of the locality of pain by animals in the laboratory leaves only the human organism as the means of evaluating the efficacy of the drug. The preparation can be used without further study because of its lack of toxicity. We have administered more than 5000 injections and there has never been any untoward local or general reaction, save a slight burning at the time of injection. It should not, however, be used in cases with parasympathetic preponderance.

Owing to the woeful lack of other than temporary palliatives for anginal crises, we felt assured that the advent of the extract would be welcomed. Our only fear is that the drug may be used with too much enthusiasm and eagerness to allow a proper appraisal of its therapeutic value. It always has been a clinical observation of ours that one's attitude in employing a new therapeutic measure somehow was sensed by the patient and reflected in his or her reaction. We tried studiously to avoid showing our mental attitude in the hope that where the only measure of our results was the patient's own estimate of his condition, we did nothing consciously to prejudice it.

Conclusions

1. Twenty cases of angina pectoris were treated with tissue extract (antisympathone).

2. Symptomatic relief was obtained in eleven cases, six had partial relief, and three had no relief.

3. We believe that the extract is a valuable addition to the therapeutic armamentarium against angina pectoris, to be used in conjunction with all other means at our command.

4. We believe the mode of action is by sympathetic depression. It should not be used in cases with parasympathetic preponderance.

5. The preparation is non-toxic, its only contraindication being acute coronary thrombosis and the parasympathetic group of cases.

6. We urge wide clinical trial of the extract to better determine its exact value.

Note: We desire to express our indebtedness to Dr. Marie Severac, Mr. R. H. Hutchison, Mr. Arnold Quici, and Mrs. Lena Sklar for their valuable aid in certain phases of this work.

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Medulloblastoma Cerebelli*†

A Case with Autopsy: Midline Cerebellar Tumors in Children and Young Adults

By Karl Rothschild, M.D., *New Brunswick, N. J.*

BRAIN tumors and especially cerebellar tumors are so frequently seen—and so frequently overlooked—that it seems justifiable to publish a report of some unusual findings in a journal read by the internist. The present paper intends to deal with one phase of the problem, the cerebellar tumors of children and young adults.

In 1925, Bailey and Cushing[1] published an extensive study of these tumors. They report that the initial symptoms were those of increased intracranial tension of abrupt onset, starting only a few months before admission to the hospital. Only occasionally headache was present, usually attributed to some gastric upset. As further symptoms they mention: rapid appearance of choked disk; separation of cranial sutures (figures 2 and 3); history of staggering gait; ataxia, more in the lower extremities than in the upper; in a few cases cerebellar seizures with signs suggestive of basilar meningitis. Nystagmus was inconspicuous, diplopia often present, sometimes bilateral abducens palsy. Most cases occurred below the age of fifteen years. At that time the authors stated that attempts to extirpate these tumors in toto were futile and even exposure and decompression were accompanied by high mortality. "Conservative attitude is a course of wisdom." They recommend decompression followed by persistent roentgen-ray therapy. In 1927 Cushing[2] reports eleven cerebellar tumors of which the "majority have been median gliomas of one variety or another, originating from the roof of the fourth ventricle. Seven of them had a good prognosis." He reports the finding of an enlarged head with MacEwen's sign, the enlargement of the head being followed by cessation of headache and subjective freedom from discomfort but often by that time the vision began to fail. In closing his article he states: "Medulloblastoma of the cerebellum is so common a lesion in preadolescence that when a child has unexplained vomiting, enlargement of its head and gives a story of periodical unsteadiness, look at the eye grounds every week or two." Articles by Olivecrona and Lysholm[3] and by Bailey, Sosman and van Dessel,[4] published in 1926 and 1928, show that the growth of the tumors may be inhibited for a time by roentgen therapy but that the outcome has been fatal in every case.

*From the Department of Neuro-Psychiatry, St. Peter's General Hospital, New Brunswick, N. J.

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Bailey[5] in his latest article (1930) inquires into the causes of these failures. He rejects the idea that the neoplastic cells may have become radioresistant. He rather believes that the patients may have received too much roentgen ray treatment. As the method of probable choice he now recommends decompression and thorough radiation of the entire cerebrospinal axis.

Case I. The following is a case report of a child, John K., six years of age, who was admitted to my service at St. Peter's General Hospital on May 14, 1930.

Family history: Nothing unusual.

Personal history: Had chicken-pox at the age of six months, pneumonia at the age of two years, whooping-cough at the age of five years.

Present history: Four months before admission the patient fell while skating and struck his head on the ice. He got up and walked home. One week later, he complained of pain in the occipital region of the head and in the abdomen and was taken to see several physicians. Several x-ray pictures were taken and there was a long argument whether a line seen in one of the pictures represented a fracture or not.

About four weeks before admission, the boy complained of dimness of vision, and gradually became blind. On the day of admission, he was seen by Dr. Forney of Milltown, who referred him to my service.

Physical examination: A white boy, six years of age, well developed and well nourished, complaining of abdominal pain and apparently blind.

Head and neck: Head very large. Veins somewhat large and tortuous. Both pupils were enlarged, round and equal. Right pupil reacted very faintly to light, while left did not react directly, but did so when light was thrown into the right pupil. There was a very slight stiffness of the neck.

Chest: Thorax of good capacity, good expansion. Apex beat in 5th interspace, one-half finger breadth within nipple line. Sounds normal, no murmurs. Breath sounds vesicular.

Abdomen: Slightly distended, no tenderness, no masses felt.

Extremities: Good physical power.

Neurological examination: Reflexes: Tendon reflexes of legs and arms were equal and normal. For a child, they might even be considered below normal. In fact, it was difficult to elicit the arm reflexes at all. Abdominal reflexes were absent. There was an indication of a slight Babinsky's sign on the right side, but nothing definite. There was a suggestion of a bilateral Kernig's sign. There was no ataxia. Finger-finger and finger-nose tests were performed well. The child walked in a straight direction. There was no nystagmus. There were no disturbances of any cranial nerves, except the optic.

Ophthalmoscopic examination: Marked optic neuritis in both eyes, with signs of atrophy on the left side. There were many minute ruptures in the retina, showing the sclera, possibly due to suddenly increased pressure. There was also marked choroiditis of the subacute type. The right side was completely blind. The child, however, could notice a flash-light at a distance of four inches with the left eye.

Laboratory findings: Hemoglobin, 80%; leukocytes, 9,100; erythrocytes, 4,200,000. Polynuclears, 67%; small lymphocytes, 29%; large lymphocytes, 4%.

Diagnosis: In view of the amaurosis, the papilledema, and lack of other localizing symptoms, we made a diagnosis of tumor in the midline of the posterior fossa, probably of the cerebellum.

Progress notes: As the child had been in the condition in which he was brought in, for several weeks, there was no indication for hurried therapeutics, so a roentgenogram was ordered to be taken next morning, and dependent on the picture, we considered the possibility of doing a cisternal puncture.

In the morning, the child became rather restless, was crying, and it was impossible to take the roentgenograph. While I was seeing another patient in the children's ward, I was called to see the boy, who had been stricken suddenly by a seizure of not very definite symptomatology. There was frothing at the mouth, incontinence of the rectum,

slight deviation of the eyes to the left, and of the head to the right, absence of reaction of the pupils which were equal and myotic, marked cyanosis of ears and fingers.

Heart sounds were irregular and faint; respiration was irregular, of a staccato type, about six per minute.

It was deemed advisable to do a spinal puncture. We obtained a clear fluid, under about 12 mm. pressure. We removed 1 c.c., and the pressure dropped to 7 mm. Cyanosis disappeared, the heart sounds became regular and louder. The respiration, however, did not improve. Withdrawal of 2 c.c. more, did not help the respiration. 1/20 gr. of alphalobelin did not stimulate the respiratory center. The respiration became slower, and ceased entirely within 3 minutes. A cisternal puncture done immediately after death showed fluid of rather viscous consistency, under normal pressure. Immediately after death, we viewed the eye grounds again, and the right eye appeared as before. In the left eye, however, the atrophy of the disks could not be seen so well, because there were acute neuritic changes, with tortuosity of the blood vessels.

Autopsy: An autopsy was performed by me with the assistance of Dr. Candella. The body was that of a male child of 6 years, well-built and well-nourished, without signs of degeneration or deficiency.

The head appeared much larger than the average; in fact, it was as large as an average adult's head. The circumference was 24½ cm. in the longest diameter.

The scalp was removed in the usual way. On removing the skull, it was noticed that the sutures were widened to about 6 mm. Between these sutures, there were two different layers of bone, filling the gaps. It appeared that these insertions had been produced at different times.

The inner aspect of the bone showed many impressions, in fact, there was a true picture of the external architecture of the brain impressed on the bone (convolutional atrophy). Dura was removed easily. Pacchioni's granulations were normal in number, but enlarged. The sinuses within the dura were widened. There were no signs of old or recent infections of the arachnoid or pia membranes.

The brain was removed in toto, by a section which included as much of the oblongate medulla as possible. The weight of the brain was 1425 gms. The external appearance of the brain was normal. Both halves were equal in size. The cerebellum appeared slightly sub-normal in size, but its two halves were equal, and it felt soft throughout. The origins of the cerebral nerves were unobstructed. There was no pathology of the optic tracts. The oblongate medulla showed

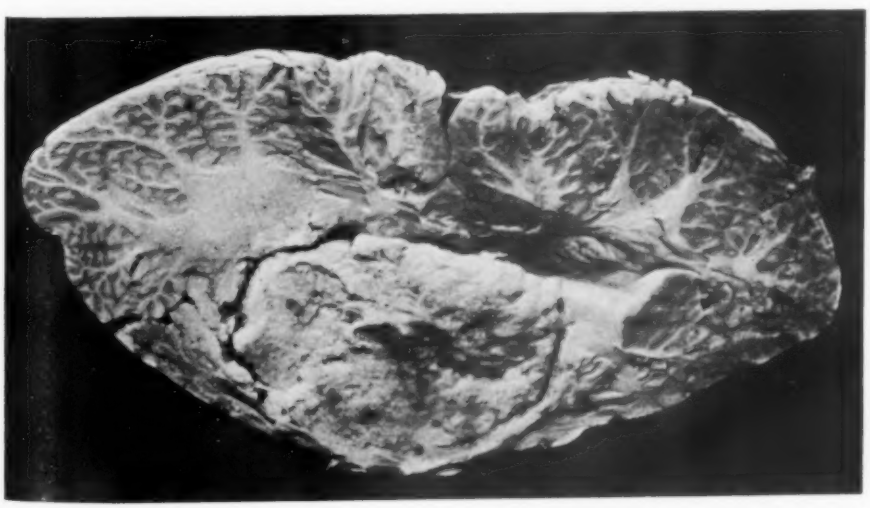

FIG. 1. Medulloblastoma of cerebellum. Note position in midline. Hemispheres are intact. No localizing symptoms. Natural size.

normal contour and architecture on transverse section.

The cortex appeared rather thin. The whole brain had a certain spongy appearance. The usual blood spots seen throughout the white substance were enlarged. The 3rd and 4th ventricles were markedly dilated, especially the 4th. The regions of the striate system and the internal capsule showed normal and regular formations.

On sectioning the cerebellum, a tumor (figure 1) was found of the size of a small hen's egg, originating from the roof of the fourth ventricle. It did not invade the hemispheres of the cerebellum, but only pushed them aside, and the impressions of the tumor were shown on the median aspects of the hemispheres.

The tumor had a spongy appearance, and there were several blood clots found in its interior, apparently originating from a very recent hemorrhage. Histological examination of the tumor proved it to be extremely cellular, without definite arrangement of the cells. In some areas there was pseudo-rosette formation around a vessel. Mitoses were occasionally seen. There was a scarcity of stroma. The vessels showed proliferative endarteritis. These findings, together with the origin of the tumor from the roof of the fourth ventricle, permitted the diagnosis of a medulloblastoma (figure 4). The tumor was derived from medulloblasts, very young bipotential cells, both spongioblasts and neuroblasts having been found throughout the tumor. (I am indebted to Dr. B. J. Alpers of Philadelphia for looking over the slides and preparing the photomicrograph).

This case was extremely interesting because there were actually no physical or neurological signs present, except enlargement of the head and slowly increasing amaurosis; the reason being that the hemispheres were not invaded but only pushed aside but well preserved in their outline, as may be well seen in figure 1. This pathology would well corroborate Cushing's description

FIG. 2. Roentgenograph of skull. Arrows point to places of secondary rewidening of sutures. Note impressions of brain on skull.

of these tumors. If the eye grounds of the child had been examined, the outcome might have been a different one. The law of *post hoc, ergo propter hoc*, certainly led the roentgenologist into over-emphasizing the value of finding a probable fracture. This child showed even fewer symptoms than are generally the rule inasmuch as there were not even vomiting or ataxia present. Increasing blindness and abdominal pain were the outstanding symptoms. What really caused the unexpected death of the child a few hours after admission to the hospital is not definitely explained. We may assume that there was a sudden hemorrhage into the tumor.

Case II. While writing this article I had admitted to my service another child, a boy ten years of age who fell sick with vomiting

FIG. 3. Antero-posterior view of figure 2.

and dizziness seventeen days ago. On admission to the hospital he showed choked disks and a slight horizontal nystagmus when looking to the right. He felt well while lying down. The deep reflexes were abolished, with possible presence of diminished left Achilles reflex and an indication of positive Babinsky's sign on the left. Finger-finger, finger-nose, and heel-knee tests were normal. Romberg's sign was positive. When sitting up, the patient became very dizzy and vomited. In this case also, I made a diagnosis of a tumor in the posterior fossa, invading the left hemisphere.

A few days after admission, the child felt considerably better, and was able to stand up and walk. He remained free from dizziness and headache. Only the choked disks remained unchanged. But after five days more, the former symptoms returned, the vision became dim and diplopia developed. The family physician later told me that there had been diplopia for two days prior to admission to the hospital.

We now had the child admitted to the neuro-surgical department of the University of Pennsylvania. Dr. Charles H. Frazier kindly reported to me that he performed the operation, after having made a diagnosis of lesion of the posterior fossa, probably involving the left cerebellar hemisphere. The operation was performed under colonic and avertin anesthesia. The posterior horn of the left ventricle was tapped and a large quantity of fluid escaped. After transverse incision, the occipital sinus was ligated. The various surfaces of the left cerebellar hemisphere were explored with negative results. No difference in size of the hemisphere was noted and no displacement of the midline. An exploratory canula was introduced into the left hemisphere with negative results.

"For these several reasons, chiefly because of the lack of displacement of the midline,

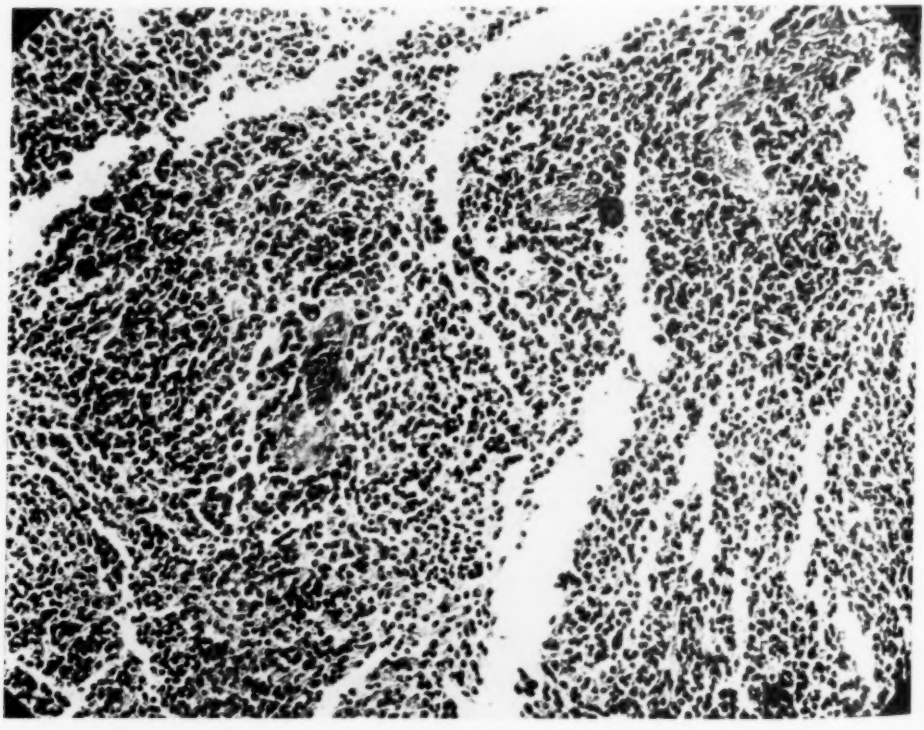

FIG. 4. Microphotograph of tumor (Case 1): Extremely cellular. Tendency to grouping of cells around blood vessels. Occasional mitoses in nuclei. Stroma sparse. (Medulloblastoma).

because the two hemispheres were of equal size, because of the extensive amount of fluid in the subarachnoid space and in the ventricles, I was disposed to regard the case as one of pseudo-tumor. It is possible, I suppose, that there may be a neoplasm of the fourth ventricle but the evidence did not seem sufficient to warrant incision of the vermis." (Dr. Frazier).

To judge from the history of the case, the free interval after an acute attack and the appearance of the roentgen plates, I am rather inclined to believe that we are dealing with a tumor. The description of Case I shows that there was in this case also no displacement of the midline, that the hemispheres were equal in size and that there was no evidence to touch of the presence of a tumor. Further developments will clear up this case. What is important from the standpoint of this paper, however, is that the diagnosis of a tumor (or a pseudo-tumor) over the original one of encephalitis was the point which decided whether this child should become blind or not. In either case, the diagnosis of involvement of the posterior fossa (by tumor or localized arachnitis) could be made from not much more than an eye ground examination.

Case III. A similar case came under my observation on April 5, 1930. The patient, Norman R., a clerk of 24 years of age, had fainted while walking in the street, had fallen, and was taken to St. Peter's Hospital. After admission, he vomited for several hours. The history dates back four years. Similar fainting spells had occurred every few months, each time while the patient was taking a walk. All attacks were accompanied by vomiting. A day or two after each attack the patient felt well again.

Neurological examination showed slight exaggeration of left biceps and triceps and absence of left abdominal reflexes. No ataxia of upper extremities. Tendency to sway toward the left when walking. Slight weakness of the left abducens. Eye grounds showed dilatation of blood vessels and choking of the disks, a little more marked on the left.

Diagnosis: Cerebellar tumor (in midline).

In this case, also, the patient improved within a few days and left the hospital in apparently good condition. I saw him four months later and he was feeling well. He refuses to be examined again, for fear, apparently, that our original diagnosis might be verified.

All of these cases had been treated before, and diagnosed as fracture of the skull (case I), encephalitis (case II) and gastric upset (case III). Judging from these experiences, it may be well to follow Cushing's advice and in cases of recurrent vomiting and dizziness, examine the eye grounds every week or two.

The material described in this paper was presented at the Scientific Exhibit of the American Medical Association at the Philadelphia session, June 1931.

References 6 to 14 represent the latest investigations on the subject.

Conclusions

1. Tumors of the cerebellum, especially medulloblastomata, are found relatively frequently in children and young adults.

2. The onset of the symptoms of medulloblastoma in this region is so insidious, and the symptoms themselves are so slightly specific that the practitioner should be directed toward considering such a tumor in cases of dizziness and vomiting of indefinite origin. Choked disks are an early sign.

3. Three cases are described, one with report of autopsy.

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Electrocardiographic Studies of the Effects of Propylene as a General Anesthetic in Man*

By Morris H. Kahn, M.A.,M.D., F.A.C.P., and Lloyd K. Riggs, Ph.D.,
New York City

THE effects of propylene, an unsaturated hydrocarbon of the olefine series, as an anesthetic in animals have been reported in a number of communications by Halsey[4,5,6] and his coworkers, by Riggs[1,2,3] and Goulden[3] and by others, with interesting and encouraging results. All have reported that propylene was an effective anesthetic in concentrations of 40 to 60 per cent by volume. None of these authors have reported either an immediate or delayed toxic action of this hydrocarbon. It appeared, therefore, that propylene might with safety be tried out in actual surgical practice.

A group of research workers in New Orleans under the leadership of Prof. Halsey of Tulane University were the first to undertake clinical trials of propylene. Two cases of appendectomy were reported, in one of which marked irregularity of the heart developed toward the end of the period of anesthesia which was maintained for a little over thirty minutes.

Gwathmey, of New York, reported the use of propylene as an anesthetic for short dental operations, and observed no unfavorable heart symptoms.

Caine[8] and Reynolds[8,9] undertook electrocardiographic studies on the action of propylene and other anesthetic gases. They found that non-anesthetic concentrations of propylene (25 per cent) caused ectopic ventricular beats which promptly disappeared when the concentration of propylene was lowered. Higher concentrations of propylene caused more frequent ectopic ventricular beats and runs of ventricular tachycardia of longer or shorter duration.

Chapman studied the action of propylene and of ethylene upon isolated turtle and frog hearts, and found that "propylene in narcotic dosage is somewhat less depressing to these cold-blooded hearts than is ethylene".

In view of the above evidence Riggs and Goulden pursued further their studies on the physiologic action of propylene, giving special attention to its action upon the heart, and studying carefully the mechanism of death, watching the time of the cessation of respiration and of the heart beat. They employed cats, dogs, guinea-pigs and rabbits. Their results tended strongly to confirm their previous observations that the primary toxic action of propylene is upon the respiratory center, and quite secondarily upon the heart.

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Method of Electrocardiographic Study

In view of these studies it appeared desirable to proceed with electrocardiographic studies on the human subject under propylene anesthesia. Dr. Lloyd K. Riggs offered himself as the subject of these experiments which were carried out at the Beth Israel Hospital in New York City. Dr. Riggs submitted himself to general anesthesia two or three times each day that the experiments were conducted, at intervals sufficient to permit the dissipation of any possible overhanging effects from one period of anesthesia to the next. The experiments were conducted at weekly intervals, and the anesthetic was administered two or more hours after a light meal but with no other preparation.

A length of rubber tubing held in the patient's hand was connected to a tambour and indicator which swung in front of the slit of the camera of the electrocardiograph. This was used to indicate each inspiration of the patient until he became unconscious, and again his respirations when he remembered to signal as he recovered from the anesthetic.

At first continuous records were taken in either Lead 1, 2 or 3 as indicated in the tables. Subsequently it was considered equally adequate, during more prolonged anesthesia, to take short strips of record at definite intervals of one-quarter to one minute. Very careful analyses were made of the electrocardiographic films under the following headings:

1. The intervals between respirations, from the first exhibition of the anesthetic until anesthesia was complete.

2. Adding these, we ascertain the length of time it required for propylene to anesthetize the patient.

3. The R-R interval in seconds indicates the rate of the heart beat in very exact figures.

4. The P-R interval indicates the conduction period in the heart and suggests the central nervous effects of propylene upon the heart mechanism.

5. Other miscellaneous effects, if and as they are encountered.

Method of Anesthesia

Propylene had been freshly prepared the day previous to the experiments in various concentrations and was administered under atmospheric pressure by displacement with water. At first it was used in a freshly prepared mixture consisting of propylene 40 per cent, oxygen 20 per cent and the rest nitrogen. This applies to Experiments 1 and 2. In Experiments 3, 4 and 5 we used propylene 50 per cent, oxygen 20 per cent and nitrogen 30 per cent. In experiment 6 we used 75 per cent propylene and 25 per cent oxygen. In Experiments 7, 8, and 9 we used 50 per cent propylene, 20 per cent oxygen and 30 per cent nitrogen.

In every case the anesthesia was maintained for a period of a few minutes, and in the last experiment it lasted 16 minutes.

General Effects of the Anesthetic

During administration of propylene, in all but the last experiment, the respirations continued entirely regular as is indicated in the tables by the time

intervals between respirations. After the first few breaths, there was usually slight reddening of the eyelids with some lacrimation and flushing of the face. This was more marked with a high concentration of the anesthetic. Apparently the irritation was more than conjunctival as sometimes coughing would occur from pharyngeal irritation. Just before the patient became unconscious there was noted contraction of the left leg and sometimes also flexion of the right leg which quickly subsided and the legs would remain entirely limp. Otherwise the progress of the anesthesia was uneventful and gradual, and after an average period of ten breaths anesthesia was complete. During this time pinching or sticking the patient with a pin indicated complete insensitiveness. The tables 1 to 9, show the rapidity with which the anesthesia produced unconsciousness.

TABLE I
ANALYSIS OF EXPERIMENT I

Progress of the Experiment	Duration of Signal	Intervals between Inhalations	R-R Interval	Heart Rate	P-R Interval
Before Signal			.6-.72	83-100	.16 sec.
1st Inhalation	1.4 sec.	7.0 seconds	.6-.66	91-100	
2nd "	.9 "	7.0 "	.6-.68	88-100	
3rd "	2.0 "	7.0 "	.7-.65	86- 92	
4th "	1.8 "	7.0 "	.6	100	
5th "	.9 "	7.0 "	.6	100	.16 "
6th "	.4 "	6.0 "	.56	107	
7th "	.4 "	5.5 "	.56	107	
8th "	.2 "	6.0 "	.56	107	
9th "	.7 "	5.1 "	.56	107	
Anesthesia complete after 57.6 seconds.					
During Anesthesia			.56	107	.16 "
Recovering from Anesthetic-Onset			.6-.66	91-100	.14 "
After ½ minute			.6-.66	91-100	.16 "
After 1 minute			.68-.72	83- 88	.20 "
After 2 minutes			.76	79	.20 "

Remarks: Lead 3 used. Pulse was good and unchanged throughout. Face flushed. Recovering signal given by patient 1 minute after removal of mask; duration of signal was 0.6 second. Propylene 40%, Oxygen 20%, and Nitrogen 40%.

TABLE II
ANALYSIS OF EXPERIMENT II

Progress of the Experiment	Duration of Signal	Intervals between Inhalations	R-R Interval	Heart Rate	P-R Interval
Before Signal			.68	88	.14 sec.
1st Inhalation	1.2 sec.	3.6 seconds	.7	86	
2nd "	1.9 "	5.2 "	.68	88	
3rd "	2.0 "	5.0 "	.66	91	
4th "	2.4 "	5.2 "	.64	93	
5th "	1.0 "	4.6 "	.64	93	
6th "	.6 "	5.6 "	.68	88	.16 "
7th "	2.4 "	5.6 "	.64	93	
8th "	2.6 "	5.0 "	.64-.68	88-93	
9th "	2.0 "	5.4 "	.68	88	.16 "
10th "	2.2 "	5.0 "	.68	88	
11th "	2.2 "	5.4 "	.64-.72	83-93	
12th "	2.4 "	9.4 "	.68	88	
Anesthesia complete after 65.0 seconds.					
During Anesthesia			.72-.78	77-83	
Recovering from Anesthetic-Onset			.72	83	.16 "
Signal after ½ minute			.70	86	

Remarks: Lead 2 used. Propylene 40%, Oxygen 20%, Nitrogen 40%. Recovering signal given by patient ½ minute after removal of mask; duration of signal 1.6 second.

TABLE III

ANALYSIS OF EXPERIMENT III

Progress of the Experiment	Duration of Signal	Intervals between Inhalations	R-R Interval	Heart Rate	P-R Interval
Before Signal			.64-.68	88- 93	.16 sec.
1st Inhalation	2.2 sec.	5.0 seconds	.8	75	.16 "
2nd "	1.8 "	5.0 "	.7	86	
3rd "	2.0 "	5.2 "	.66	91	
4th "	1.2 "	4.4 "	.68	88	.16 "
5th "	3.0 "	6.0 "	.64	93	
6th "	3.6 "	7.2 "	.6	100	.16 "
7th "	2.2 "	5.2 "	.6	100	.16 "
Anesthesia complete after 38 seconds					
During Anesthesia			.56-.6	100-107	.16 "
Recovering from Anesthetic-Onset			.64	93	.16 "
Signal after ½ minute			.72	83	
After 1 minute			.72	83	

Remarks: Lead 2 used. Propylene 50%, Oxygen 20%, Nitrogen 30%. First return of consciousness was indicated by the signal.

TABLE IV

ANALYSIS OF EXPERIMENT IV

Progress of the Experiment	Duration of Signal	Intervals between Inhalations	R-R Interval	Heart Rate	P-R Interval
Before Signal			.74-.78	77- 81	.14-.16 sec
1st Inhalation	0.8 sec.	4.0 seconds	.72	83	.14 "
2nd "	0.4 "	5.0 "	.74	81	
3rd "	1.0 "	5.0 "	.68	88	.14 "
4th "	0.4 "	5.2 "	.68	88	
5th "	0.6 "	5.0 "	.60-.64	93-100	.16 "
6th "	0.6 "	4.8 "	.60	100	.16 "
7th "	0.4 "	4.6 "	.60-.62	97-100	
Anesthesia complete after 33.6 seconds.					
During Anesthesia			.66	91	.14-.16 "
Recovering from Anesthetic					
Signal after ½ minute			.62-.66	91- 97	.14-.16 "
1 minute after			.76	79	.14 "

Remarks: Lead 2 used. Complete anesthesia was maintained for about two minutes. Propylene 50%, Oxygen 20%, Nitrogen 30%.

TABLE V

ANALYSIS OF EXPERIMENT V

Progress of the Experiment	Duration of Signal	Intervals between Inhalations	R-R Intervals	Heart Rate	P-R Intervals
Before Signal			.68-.72	83- 88	.14-.16 sec.
1st Inhalation	1.6 sec.	5.6 seconds	.72	83	.16 "
2nd "	1.0 "	5.2 "	.76	79	
3rd "	2.0 "	5.6 "	.64	93	.16 "
4th "	2.0 "	5.4 "	.62	97	.16 "
5th "	1.6 "	5.6 "	.60	100	
Anesthesia complete after 27.6 seconds.					
During Anesthesia			.58-.60	100-104	.14-.16 "
Recovering from anesthetic after 1 minute			.74-.80	75- 81	.14-.16 "

Remarks: Lead 2 used. Propylene 50%, Oxygen 20%, Nitrogen 30%.

TABLE VI
ANALYSIS OF EXPERIMENT VI

Progress of the Experiment	Duration of Signal	Intervals between Inhalations	R-R Intervals	Heart Rate	P-R Intervals
Before Signal			.72	83	.16 Sec.
1st inhalation	1.0 sec.	5.2 seconds	.72	83	
2nd "	2.6 "	5.2 "	.68	88	
3rd "	2.2 "	5.6 "	.68	88	.16 "
4th "	2.4 "	5.4 "	.72	83	.16 "
5th "	2.0 "	5.6 "	.72	83	.16 "
6th "	3.0 "	6.8 "	.72	83	
7th "	2.4 "	6.4 "	.72	83	
8th "	2.8 "	6.6 "	.70	86	.16 "
9th "	2.6 "	7.0 "	.68	88	
10th "	2.4 "	6.0 "	70	86	
11th "	2.4 "	6.0 "	.72	83	.16 "
12th "	3.0 "	6.2 "	.64	97	
13th "	2.4 "	5.2 "	.7	86	
Anesthesia complete after 77.2 seconds.					
During Anesthesia			.68	88	.16 "
Recovering from Anesthetic-Onset			.70	79	.16 "
½ minute after			.72	83	.16 "
1 minute after					
1st signal	1.6 sec.	5.0 "	.70-.82	73-79	
2nd "	1.6 "	5.2 "	.74-.76	79-81	
2 minutes after					
3 minutes after			.72	83	
4 minutes after			.72-.76	79-83	.16 sec.

Remarks: Lead 2 used. Propylene 75%, Oxygen 25%. There were slight twitches of the left leg and right shoulder and movements of the head, then swallowing movements and watering of the conjunctivae.

TABLE VII
ANALYSIS OF EXPERIMENT VII

Progress of the Experiment	Duration of Signal	Intervals between Inhalations	R-R Intervals	Heart Rate	P-R Intervals
Before Anesthesia Leads 1, 2, 3.			.72-.76 sec.	79- 83	.14 sec.
Before Signal			.64 "	93	.12-.16 "
1st Inhalation	0.8 sec.	5.0 seconds	.64	93	
2nd "	1.0 "	6.0 "	.68	88	
3rd "	0.6 "	5.4 "	.70	86	.14 "
4th "	1.6 "	5.2 "	.68	88	
5th "	1.6 "	6.2 "	.64-.66	91- 93	.14 "
6th "	2.8 "	6.2 "	.62	97	
7th "	2.0 "	6.6 "	.60	100	.12-.14 "
Anesthesia complete after 40.6 seconds.					
During Anesthesia-after ½ minute			.64	93	.12-.14 "
" 1 minute			.70-.72	83- 86	.14 "
" 2 minutes			.85	71	.12 "
" 3 minutes			.76	79	.14 "
" 4 minutes			.70	86	
" 5 minutes			.68	88	
Recovering from Anesthetic—First signal			84	72	.14 "
After 1 minute			.80	75	.14 "

Remarks: Lead 2 used. Propylene 50%, Oxygen 20%, Nitrogen 30%.

TABLE VIII
ANALYSIS OF EXPERIMENT VIII

Progress of the Experiment	Intervals between Inhalations	R-R Intervals	Heart Rate	P-R Intervals
Before Signal		.74-.76	81- 83	.14 sec.
1st Inhalation	6.0 seconds	.68	88	
2nd "	6.0 "	.64	93	
3rd "	6.6 "	.66	91	
4th "	6.2 "	.64	93	.14 "
5th "	6.2 "	.60	100	
Anesthesia complete after 40 seconds				
After 1 minute		.60	100	.14 "
" 2 minutes		.68-.70	86- 88	.16 "
" 3 "		.72	83	.16 "
" 4 "		.76-.82	73- 83	
" 5 "		.80-.84	72- 75	
" 6 "		.84-.92	65- 85	.14 "
Recovering from Anesthetic				
First Signal		.72-.74	81- 83	
After 1 minute		.72-.74	81- 83	

Remarks: Lead 2 used. Propylene 50%, Oxygen 20%, Nitrogen 30%. During complete anesthesia strips of record were taken at intervals of one minute until patient regained consciousness.

	.64-.68	88- 93	.16 sec.

TABLE IX
ANALYSIS OF EXPERIMENT IX

Progress of the Experiment	Intervals between Inhalations	R-R Intervals	Heart Rate	P-R Intervals
Before Signal		.72	83	.14 sec.
1st Inhalation	5.0 seconds	.76	86	
2nd "	5.0 "	.72	83	
3rd "	6.0 "	.72	83	
4th "	6.6 "	.72	83	
5th "	4.4 "	.66	91	
6th "	4.8 "	.68	88	
7th "	4.8 "	.68	88	
8th "	5.8 "	.64	91	.14 "
Anesthesia complete after 42.4 seconds.				
During complete anesthesia-Onset		.68	88	.14 "
After 1 minute		.70-.76	81-86	
" 2 minutes		.82	73	
" 3 "		.84	72	
" 4 "		.86	70	
" 5 "		.76	81	
" 6 "		.78	77	
" 7 "		.74-.76	81-83	
" 8 "		.78	77	
" 9 "		.78-.80	75-77	
" 10 "		.78-.80	75-77	
" 11 "		.78-.82	73-77	
" 12 "		.84	72	
" 13 "		.84	72	
" 14 "		.80-92	65-75	
" 15 "		.76	81	
" 16 "		.76-.80	75-81	
Patient suddenly ceased to breathe for 40 to 60 seconds, then he gasped, and soon recovered. The heart beat remained unchanged.				
Recovering from the Anesthetic		.80	75	.14 "

Remarks: Lead 2 used. Propylene 50%, Oxygen 20%, Nitrogen 30%. Depression of the respiratory center occurred with cessation of breathing for about one minute, while the heart beat was not appreciably affected.

During anesthesia in all but the last experiment the patient's breathing continued regular. There was no further lacrimation nor any movement of skeletal muscles until the commencement of recovery from the anesthetic. With that, the patient gradually opened his eyes, looked about him, smiled, swallowed, drew his right hand up to his mouth with a motion as if to wipe his lips, and felt for the tubing of the signal to press; that being apparently the prompt recollection. The return of the signal on the film was a suitable indication of returning consciousness. There was no feeling of nausea or vomiting during any of the experiments, and no feeling of any illness at all. After a maximum of two minutes from the removal of the anesthetic, consciousness was complete. The patient desired to sit up and inquired how the anesthesia had progressed.

Electrocardiographic Effects of Propylene

A preliminary electrocardiographic study was made before each experiment to ascertain the normal status of the individual. The electrocardiogram of Dr. Riggs was entirely normal, with moderate voltage, showing all the waves upright in the three leads, of normal duration and normal time relations, and fairly well marked sinus arrhythmia.

During the progress of the anesthesia the sinus arrhythmia became less distinct. We consider this, as shown by the graph (figure 1), a quite definite effect of propylene. In no experiment was there evidence of any sudden change of rate, except that resulting from the lessened sinus arrhythmia. In each of the experiments, when the patient aroused from the anesthesia, the pulse rate was two to ten beats lower

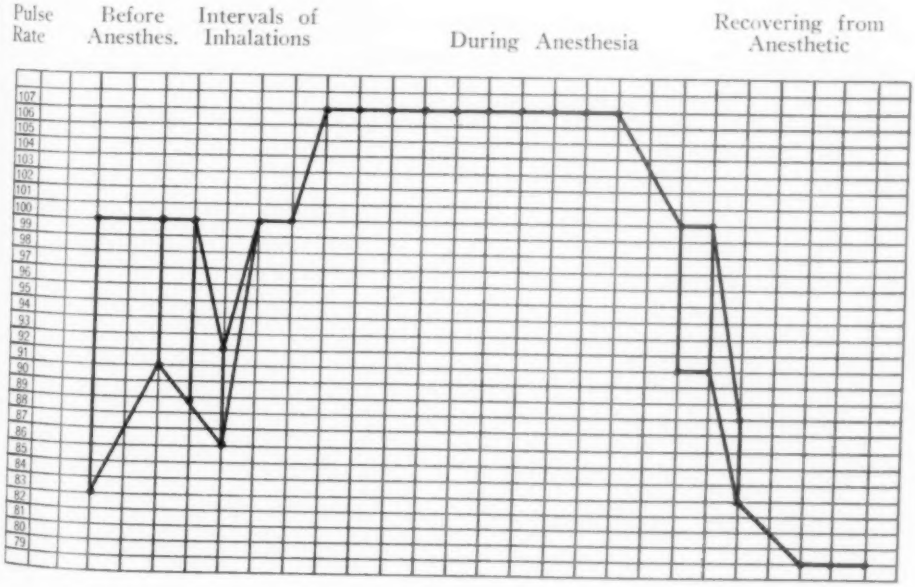

Fig. 1.
Graph showing the effect of propylene anesthesia on sinus arrhythmia.
(From experiment I.)

than at the beginning of the anesthesia. The rate and the sinus rhythm returned to their original status within a few minutes after recovery from anesthesia. The character of the waves and the voltage remained unchanged during the experiments. No aberrant conduction tract was noted in any films, and no premature beats or any other form of irregularity occurred.

Summary and Conclusions

Electrocardiographic studies were made on the human subject of the effects of propylene as a general anesthetic. From their previous experimental work with animals Riggs and Goulden had come to the conclusion that the primary toxic action of propylene is upon the respiratory center, and quite secondarily upon the heart. The present study corroborates this conclusion for the human subject as well.

Propylene used as a general anesthetic in man produces complete anesthesia after an average of eight inhalations. There occurs no struggling or any reactive symptoms during the period of induction. During complete anesthesia the breathing is quiet and regular. The heart remained uninfluenced by the anesthetic except for a diminution of sinus arrhythmia during complete narcosis. The pulse rate and the character of the pulse as well as the electrocardiogram remained unchanged. Recovery from the anesthetic was prompt in each instance, with remarkably immediate return of memory, the patient promptly pressing his hand signal, believing that he was "still going under" after even ten minutes of complete anesthesia.

The quicker induction resulted when the mixture contained 50 per cent of propylene.

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Editorials

HEREDITY OF ELLIPTICAL ERYTHROCYTES (OVALOCYTOSIS)

An interesting sequel has appeared to a study which was published in the ANNALS in 1929 of a family showing elliptical erythrocytes. In this paper by Hunter and Adams[1] personal observations were reported of three generations of a family of Dutch extraction, one member of which was living in Portland, Oregon, and the others near Missoula, Mont. Twelve members of this family were found to exhibit the anomaly in question, consisting of the presence in the circulating blood of elliptical, elongated and irregularly shaped erythrocytes. Differences were recognized and established between this condition and the more common sickle cell anemia. Several members of the family were more or less anemic and one showed a marked anemia, which improved under liver therapy. The twelve individuals showing the anomaly were members of three generations: a grandfather; each of his eight children, five boys and three girls; and three of six grandchildren, a boy and two girls, who were children of two daughters in the second generation. Prior to the emigration of the grandparents to this country none of the family, as far as known, had ever been outside the boundaries of Holland. For generations, the men were farmers and lived in the village of Zevenhuisen, near Amsterdam. This paper attracted the attention of Professor A. A. Hymans van den Bergh of the University of Utrecht, not only because it added a considerable number of new cases of this anomaly in which he was already interested, but also because the family was of Dutch extraction. He accordingly obtained the family name from the American authors and through a member of his staff investigated the branches of the family still resident in Holland. The results of this search have now been published[2]. Although the investigation was rendered difficult and in part incomplete because of the dispersion of the family and the refusal of certain of the parents to permit examination of their children, four additional examples of the anomaly were discovered. It was learned that the branch of the family in America had originated from the third marriage of the great grandfather, who had been married four times. From the first marriage there was no issue. Among the descendants in the lines resulting from the second and fourth marriages there was not a single example of elliptical erythrocytes.

[1] HUNTER, WARREN C., and ADAMS, RICHARD B.: Hematologic study of three generations of a white family showing elliptical erythrocytes, Ann. Int. Med., 1929, ii, 1162-1174.

[2] VAN DEN BERGH, A. A. HYMANS: A propos des hématies elliptiques (l' ovalocytose), Rev. Belge d. Sci. Med., 1931, iii, 683-688.

It therefore was evident that the anomaly had been introduced by the third wife. Accordingly, the investigation was broadened to include her collateral lines. It was found that she was one of seven children, all deceased, but only certain of the children of one of her sisters could be examined. In this family of eight children, three of the five examined were found to have elliptical red blood cells. A daughter of one of these made the fourth example in this line, and the sixteenth in the combined group. It is unfortunate that the numerous other collateral lines could not be investigated. From the combined genealogical charts of Hunter and Adams and of van den Bergh, it is shown that in this family the condition of having elliptical erythrocytes is inherited as a dominant trait, appearing only in the offspring of affected individuals and is transmissible by either sex. This affords another striking example of the inheritance of a hematic condition.

SIGNIFICANCE OF POSITIVE ASCHHEIM-ZONDEK TEST IN THE MALE

The biological relationship between host cells and tumor cells in patients with malignant teratomas of the testis containing chorionic epithelial structures is unlike that which can occur in the male under any other circumstances. If the included blastomere theory of the origin of complex teratomas of this type is accepted, it means for the male that in his testis there is growing a structure composed in part of the fetal components of the placenta belonging to his included twin brother. The adult male body is thus subjected to hormonal influences normally experienced only by the female. That significant hormonal activity attaches to this neoplasm has been known for a good many years. Enlargement of the breasts is an extremely common finding with testicular chorio-epithelioma (malignant syncytioma), so that the examining physician has utterly failed in his duty to his patient if he does not make a careful examination of the testes when confronted by gynecomastia. If no intrascrotal tumor is found, but one testis is undescended, the cryptorchid is under a special burden of suspicion. If histological examination of the breast is possible, it will be found that the gynecomastia is of the type of a functional hypertrophy rather than the excessive fattiness of the enlarged breasts of pituitary dystrophy. There is clinical evidence of a quantitative relationship between the amount of living chorio-epithelial neoplasm and the degree of hormonal activity. In an instance known to the writer a surgeon removed a male breast showing marked enlargement due to functional hypertrophy. At the suggestion of a pathologist he enlarged his field of physical examination and found a testicular neoplasm which, when removed, proved to be in part chorio-epitheliomatous. The remaining breast, which was enlarged, but to a less marked degree than the one removed, decreased to about normal size before the patient left the hospital. However, when he returned a number of months later with innumerable metastases, all of which showed the usual mélange of syncytial cells and those from the Langhans' layer, the remaining breast

had reached a size larger than that of the other at the time it was amputated. This constituted an unintentional, but none the less controlled, biological experiment.

Further evidence of the hormonal aspect of this neoplasm rests on the occasional observation that after the removal of a primary chorio-epithelioma, its secondaries may undergo spontaneous retrogression. Unfortunately, this is apparently a rare occurrence which is limited to the less malignant forms and has been described only for the similar tumor in the female following pregnancy, in which the genetic relationship between host cells and neoplasm cells is more remote.

It is not surprising, in view of these clinical evidences, that a biologic means of detecting this hormone should be found in the Aschheim-Zondek reaction for the recognition of the presence of Prolan A. A summary of the scant earlier data on this subject and considerable new evidence are found in an extremely interesting paper by Ferguson and his associates[1] at the Douglas Research Laboratories of the Memorial Hospital, New York City. The question is complicated by the occurrence of positive reactions in the presence of carcinoma in the female, especially of genital carcinoma. Thus Zondek found forty-five positive reactions among fifty-five cases of genital carcinoma in non-pregnant women, and five positive reactions in a group of fourteen women with extragenital carcinoma. At the time when Ferguson's paper was written Zondek had reported upon a group of men with extragenital carcinoma, thirty in all, of whom four gave positive reactions; and upon a group of four men with genital carcinoma, of whom two with carcinoma of the prostate gave negative reactions and two with neoplasms of the testis, not verified histologically, gave positive reactions. Heidrich and Fels had found a positive reaction in a man, thirty-five years old, with a proved chorio-epithelioma of the testis. Ferguson and his group found negative reactions in fifteen men with normal testes, including three who were normal and twelve with extratesticular carcinoma. Negative reactions were found also in twenty-four with non-malignant lesions of the testes, only one of which was a blastoma. Eight cases with testicular teratoma all gave positive reactions. Of four cases of teratoma without clinical evidence of disease for three months to three years, three had negative reactions and the fourth who had had the right testis removed ten years before under a diagnosis of sarcoma and the right testis removed three months before for a proved embryonal carcinoma, gave a positive reaction. The suggestion is made by the authors that a lack of balance of the hormone of the anterior hypophysis due to his castrate condition might explain the positive reaction of this eunuch; but certainly insufficient time had elapsed to eliminate the possibility of subclinical metastasis. From the results reported, it would seem that the Aschheim-Zondek reaction provides a re-

[1] Ferguson, Russell S.; Downes, Helen R.; Ellis, Edward, and Nicholson, Mary E.: Preliminary note on a new method of differentiating the testicular tumors by biological means, Am. Jr. of Cancer, 1931, xv, 835-843.

markably consistent method of determining the presence of malignant tumors of the testis at an early date (43 days from the known date of onset in one instance) in the course of the disease. The importance of this in differential diagnosis and in the presence of cryptorchidism can readily be appreciated. From the results available this reaction does not appear to differentiate chorio-epithelioma from other forms of malignant teratoma of the testis. It would require serial sections of the entire growth, however, to rule out beyond any doubt, the possibility that malignant syncytioma was present. It is probably that most, if not all, testicular teratomas are originally trigerminal and that one or more cell types, acquiring the attributes of malignancy, outgrow all of the others.

A still broader significance may attach to this line of investigation. Normal chorionic syncytium and cancer cells have much in common: extraordinary reproductive energy, rapidity of growth, invasive power coupled with destruction of the recipient tissue, and striking facility for hematogenous dissemination. When chorionic syncytial giant cells lodge in the lung, as they do with every childbirth, they soon die; but when carcinoma cell emboli lodge in the lung, they survive and grow only too frequently. One succumbs, apparently, to an anti-syncytial hormone; against the other no such defensive mechanism seems to be at hand. The Aschheim-Zondek reaction, or modifications of the same principle, may eventually give much information about the biologic relationship of the cancer cell to its host tissue, as it affects the hormonal balance of the entire organism.

Abstracts

The Diagnostic Program in Food Allergy. By WARREN T. VAUGHAN, M.D. (Am. Jr. Med. Sci., 1931, clxxxii, 459-467.)

From the past history, and the family history, the probability of the existence of an allergic state can usually be determined; and the history of each attack may, if carefully gone into, furnish good clues to foods which should be suspected. Thorough physical examination and careful laboratory investigation must be utilized in order to recognize such associated organic diseases as may be present. Both the scratch method and the intradermal technic have a distinct place. The latter is much the more sensitive but should not be done without preliminary scratch studies. If the skin tests are negative or if, after trial, it is learned that all of the allergenic foods have not been discovered, two other methods of study remain. If the symptoms manifest themselves at intervals of several days, the *food diary* in which the patient tabulates all substances which he ingests and notes the appearance of allergic manifestations may reveal the offending substances. If the symptoms are fairly constant or appear at frequent intervals, the *trial diet* may be of the greatest value. In this connection the author emphasizes the importance of giving due regard to the biological grouping of food substances. When one member of a botanical food group has been proven allergenic to an individual, other members of the same group may cause allergic symptoms, even though their skin test reactions have been negative. Sometimes a positively reacting member of a group is found to give rise to no symptoms whatsoever, while a negatively reacting member of the same group does cause trouble. However, if one is sensitive to one member of a group, it does not necessarily follow that all other members will produce symptoms. On the background of these various considerations, a basic list of foods for use in the formulation of the trial diet is proposed. Any such diet must be followed rigorously for at least two weeks before one can be certain of the results.

I. Anemia of Dogs Produced by Feeding of the Whole Onions and of Onion Fractions. II. Anemia in Dogs Produced by Feeding Disulphide Compounds. By O. M. GRUHZIT, M.D., (Am. Jr. Med. Sci., 1931, clxxxi, 812-815; 815-820.)

The feeding of raw or autoclaved onions or their juice to adult dogs resulted in a severe anemia, confirming the findings of Sebrell in this respect. The animals were fed both the raw and the autoclaved onions in daily doses of 15 gm. per kilogram of body weight, and the onion juice in equivalent amounts of 10 cc. per kilogram. Uniform results were obtained from the three forms of feeding. Severe reduction in the number of red cells and in the hemoglobin occurred on the seventh or eighth day, when six feedings of onion had been given. There was a simultaneous increase in the white cell count. Hemolysis must play an important part in the red cell destruction for the blood serum became red with hemoglobin. In every case, following the maximum red cell destruction, the animal developed tolerance to onion in any of the three forms administered so that further feeding had no effect on the blood elements. The feeding of the steam distillate of fresh onions and of the residue from the distillation of onions caused little or no change in the blood of dogs, although the distillate possessed an extremely strong odor of onions; and dried onion juice was less effective than the juice itself. It was believed that the active agent in producing the observed effects was probably oil of onions of which allyl propyl disulphide is the chief constituent. Since this compound was not available, closely related substances containing the disulphide linkage were tried. It was found that n-propyl disulphide and di-p-tolyl disulphide caused

severe anemia in dogs through a hemolytic action upon the red cells. The rapid hemolysis was followed by a high degree of leukocytosis and marked signs of red cell regeneration. The benzyl disulphide, although isomeric with the di-p-tolyl disulphide, lacks entirely the hemolytic action of the latter. Repetition of a course of treatment with n-propyl disulphide showed no evidence of the acquisition of tolerance such as followed onion feeding.

Autopsy Observations on One Hundred and Sixteen Cases of Malignant Disease, in Eighty-Nine of Which Experimental Injections of Suprarenal Cortex (Coffey-Humber) Were Given. By HOWARD A. BALL, M.D., (Am. Jr. of Cancer, 1931, xv, 1352-1360.)

The 116 cases of malignant disease used in this study were divided into three groups; a *basic control series* composed of 25 cases of malignant disease, previously examined post-mortem by the author, in which application had been made for extract injection, but in which death had occurred before any extract was administered; a *relative control series* consisting of 47 cases receiving from 1 to 15 injections, or not more than 10.5 c.c. of the experimental adrenal cortex extract; and an *experimental observation series* consisting of 42 cases in which more than 15 injections, or more than 10.5 c.c. of the extract, had been given. Since necrosis and sloughing were the chief anatomical changes claimed by Coffey and Humber in their patent application, these manifestations were watched for especially. Necrosis and sloughing were observed frequently and occasionally seemed to be of greater degree or further extent than one would be led to expect from observation of similar uninjected cases. They occurred, however, without correlation to the total amount of extract injected and the difference in these respects among the three series was too slight to be significant. Likewise no essential difference in the incidence of necrobiosis was found on microscopical examination, using nuclear fragmentation and "replacement fibrosis" as criteria. In 28 per cent of the 89 cases which had received the extract, metastases were found in the adrenals themselves. No essential change from the usually observed characteristics of malignant tissue in far advanced cases could be determined in the two series that received the experimental suprarenal cortex extract (Coffey-Humber), and there were no significant differences between the series that had received less than 15 injections and that which had received more than that amount of treatment.

Extensive Atrophy of Subcutaneous Fat Following the Repeated Injections of Insulin. By JOHN R. WILLIAMS, M.D., F.A.C.P. (Jr. Lab. and Clin. Med., 1931, xvi, 1911-1197.)

That it is important for the patient self-administering insulin to vary the site of the injection, and equally important for the physician to make occasional physical inspections of the regions used, is shown by the increasing group of cases in which local atrophy of the subcutaneous fat occurs. The author reports and illustrates such a case. A woman, aged forty-four years, who had been taking two doses of insulin daily for nearly three years remarked upon the hollows in her thighs. Examination revealed a marked atrophy of the subcutaneous fat on the anterior surfaces of both thighs. The atrophic areas were irregular in shape and from 8 to 15 cms. in diameter with the longer axis parallel to that of the thigh. These cavities were from 2 to 3 cms. deep and gave the impression that the fat had been completely excavated from beneath the skin of the involved areas, for the muscles and blood vessels beneath could be distinctly felt. There was no evidence of soreness or inflammation. Similar changes were noticed in a girl who was taking four small doses of insulin daily. In this case, after avoiding injection of the areas of atrophy for some time the defects disappeared, apparently being filled in by new fat. The cause of this unusual atrophy is unknown, but a low grade inflammation with fibrosis may be the important factor.

Provisional Birth, Death, and Infant Mortality Figures, Birth Registration Area. 1930. (Public Health Reports, 1931, xlvi. 2373-2376.)

The Department of Commerce, through the Bureau of the Census, Division of Vital

Statistics, announces that in 1930 in the birth registration area (exclusive of Utah) there were reported 2,190,047 live births. This is an increase of 1.5 per cent over the number reported from the same area in 1929. Birth rates were higher in 26 states in 1930 than in 1929. In both years New Mexico has had the highest birth rate of any state, while Oregon has had the lowest rate in each of the two years under comparison. In the birth registration area (exclusive of Utah) the death rate in 1930 was 11.3. This is 0.6 lower than for 1929. The infant mortality rate for 1930 was 64.2, the lowest since the establishment of the birth registration area in 1915. In thirty-seven states an infant mortality rate was attained lower than that of the preceding year.

Carcinoma of the Stomach in a Negro of Twenty-Four Years. By JAIME DE LA GUARDIA. United Fruit Company, Medical Department, Nineteenth Annual Report, 1930, 144-148.

The occurrence of an advanced scirrhous carcinoma of the stomach in a Haitian negro 24 years of age is of interest from the standpoints both of age incidence and race incidence. The history revealed the onset of the condition to have antedated his entrance into the hospital and subsequent diagnosis by at least two years. A wide resection of the stomach was done with gratifying immediate post-operative results. The patient died about four months later of recurrence and generalized carcinomatosis.

Reviews

The Renal Lesion in Bright's Disease. By THOMAS ADDIS, Professor of Medicine, Stanford University; and JEAN OLIVER, Professor of Pathology, Long Island College of Medicine; Formerly Professor of Pathology, Stanford University. xi + 628 pages; 170 full page plates, 2 in color; 21 text illustrations and 1 folding table. Paul B. Hoeber, Inc., New York City, 1931.

One need not go far into this book by Addis and Oliver to realize that he has before him a work which is unusual in its straightforward objectivity. It is easy to prophesy for it an influence which may pervade medicine for a long time to come. It does more than set forth that which its title foreshadows; it points the way to a method. As did Bright in 1827 and Volhard and Fahr in 1914, the authors develop a comparison of clinical and pathological facts in order to determine the degree of correlation between them. Hence the method must be objective and it must be characterized by strict intellectual honesty. That such is the case there is abundant evidence throughout the work. Clinical methods and definitions in connection with the renal lesions of Bright's disease are first set forth, with a consideration of normality in the characteristics of the urine. More than one practitioner will be surprised to learn that the average rate of cast excretion in 74 supposedly normal medical students was 1040 per twelve hours. The pathological methods of qualitative and quantitative investigation of the renal lesions are also presented with carefully considered definitions of the terms used. The detailed clinical and pathological observations of the 72 cases used in the investigation occupy the next 350 pages. Each case is illustrated by two photomicrographs; one a low power view for general topography, the other of sufficiently high magnification to show the simpler cellular detail and especially valuable because of the wide area utilized, averaging four glomeruli to the field. The clinical and pathological observations are then correlated and a theoretical description of the course and sequence of the pathological processes developed. From this analysis a classification of Bright's disease satisfactory to both clinician and pathologist is proposed. The authors recognize as the main groups: *hemorrhagic* Bright's disease with initial, latent, active and terminal stages; *degen-*

crative Bright's disease, and *arteriosclerotic* Bright's disease. In both content and format this book is highly to be commended. One cannot but admire the courage of the publisher who dares to illustrate so profusely; for the illustrations of this book constitute an atlas of the pathology of nephritis. To both clinician and pathologist this work will be of very great value.

Gould's Medical Dictionary. By GEORGE M. GOULD, A.M., M.D.; Edited by R. J. E. SCOTT, M.A., B.C.L., M.D. Third edition, revised and enlarged, with illustrations and 173 tables. 1538 pages. P. Blakiston's Son and Company, Philadelphia, 1931. Price, in rigid fabrikoid with thumb index, $7.50; in flexible binding, plain, $7.00; with thumb index, $7.50.

This new edition of Gould's Medical Dictionary requires no introduction, for more than 800,000 copies of its predecessors in their various forms have been sold. When the "Pocket Medical Dictionary" came out in 1892 it contained 12,000 defined words. The edition immediately preceding the one now under review contained over 83,000 words and to that compilation many new terms have been added in the present revision. Certain omissions in the preceding edition, to which attention was called in a review in the ANNALS at that time, have been remedied, although it is not clear why 'blastophthoria', thus introduced, is capitalized. Preference is now given to the retention of the final *e* in that series of chemical terms from which it was dropped a number of years ago on the recommendation of the American Association for the Advancement of Science. This is in accord with present day orthography. The inclusion of an enormous store of useful information in tabular form has been an important feature in this series. Among the 173 tables in this edition there are a number of new tables of bacteria, metazoa and pathogenic protozoa; also the International Table of the Causes of Death. In the table of micro-organisms the original names are conveniently arranged in parallel columns with those of the new classification. These tables are made useful to the great majority of physicians whose bacteriology was not that of the last few years by basing the alphatbetical arrangement on the old names which are so much more familiar. Numerous illustrations add greatly to the value of descriptive definitions and those which differentiate between closely similar structures. A medical dictionary should be the most used text of both medical student and practitioner, and this new Gould will be found eminently satisfactory in every particular.

Recent Advances in Radiology. By PETER KERLEY, M.B., B.Ch. (N.U. I.), D.M.R.E. (Camb.); Assistant Radiologist, Westminster Hospital; Radiologist, The Royal Hospital for Diseases of the Chest. viii + 324 pages, 120 illustrations. P. Blakiston's Son and Company, Philadelphia, 1931. Price, $3.50, net.

The significant advances in the physical aspect of radiology, both technical and structural, are largely omitted from this book, for its purpose is to set before the general practitioner, the internist, and the surgeon, that which each must know about the present state of the subject in its clinical applications. Each must know the constantly expanding field of applicability of radiological methods of investigation, their limitations and the underlying principles in the interpretation of radiographs. This means that throughout the book the method of approach is that of correlation of the pathological changes with the radiological appearances. The present state of x-ray therapy is presented in a much compressed final chapter. Not all will agree that "the radiation treatment of malignant disease has now passed through the troublesome optimistic and pessimistic periods, and is established on a scientific basis." However, this chapter is largely free from unjustified enthusiasm for methods of treatment for specific neoplastic conditions and presents those conflicting views which show that the question is still unsettled. One of the most valuable of the many excellent features of the book is the emphasis placed upon what constitutes a suitable film for a particular purpose. Under lung, for instance, are sum-

marized the results of investigations carried on in the Royal Chest Hospital during the last five years. It was found that early tuberculosis is best seen in a film which shows the subclavian arteries, the inferior vena cava, and the normal interlobar pleura between the right upper and middle lobes. The demonstration of these three shadows or, at least, of the vascular ones, was then decided upon as an essential criterion of a suitable film. This text is a worthy addition to the Recent Advances series.

Textbook of Histology for Medical and Dental Students. By EUGENE C. PIETTE, M.D., Pathologist and Director of the Laboratory of the West Suburban Hospital, Oak Park, Illinois; Consulting Pathologist of the Chicago State Hospital, Chicago, Illinois; etc. xvi + 466 pages, 277 illustrations. F. A. Davis Company, Philadelphia, 1931. Price, $4.50, net.

We are told in the preface of this textbook of histology, intended primarily for medical and dental students, that an author must be first of all a censor, suppressing and omitting anything incomplete and doubtful. There are a number of assertions admitted here, however, which might well have been subjected to a more rigorous censorship. For instance, the statement is made that the hearts of human cadavers have been revived *several days after death* by injecting warm Ringer's solution with glucose into the coronary arteries, such hearts resuming contractions and continuing vital specific activity. Technical methods are briefly surveyed in fifteen pages in which paraffin sections are described as being cut with the knife perpendicular to the long dimension of the piece of tissue, apparently serial sections alone being considered. The celloidin sheet methods for handling paraffin sections are not mentioned. Crenated erythrocytes are said to be of the shape of thorn apples, missing the point that the thorns of the thorn apple (by which hawthorn rather than *Datura stramonium* is usually understood in this country) are not on the fruit. Various other assertions cannot be passed by without a challenge. There is far from general acceptance of the statement that there are no hemolymph nodes in man, and what reason is there for considering the intrafusal fibers of the muscle spindle as *immature* muscle fibers? Many subjects receive inadequate treatment to meet the needs of the medical students. The palatine tonsil is disposed of in six lines, while the teeth, in probable anticipation of use of the book in schools of dentistry, are granted thirty pages. This book is very well printed and the illustrations, of which none are original, are well reproduced. In view of the effort which has gone into its production, it is a matter for regret that the text does not meet more fully the needs of the student and of the hospital pathologist.

Streptococcic Blood Stream Infections. By GEORGE E. ROCKWELL, M.A., M.D.; Associate Professor of Bacteriology, College of Medicine, University of Cincinnati; Member of Senior Medical Staff, Bethesda Hospital; Assistant Director of Bacteriological Service, General Hospital of Cincinnati. ix + 73 pages. The MacMillan Company, New York City, 1931. Price $1.75.

This short monograph discusses streptococcic blood stream infections under eight chapter headings: Infection, Resistance, the Streptococci, the Patient, the Diagnosis, the Blood Culture, and the Treatment. The presentation of this material is far from exhaustive, the content not exceeding that which might be reasonably required of a medical student. There are frequent misspellings of such ordinary terms as 'aldehyde', 'tonsillitis', and 'cholecystitis'; and marked inconsistency in orthographic style. Words of the series having the root '$\alpha\iota\mu\alpha$' at the beginning, such as *hemolysis*, are spelled with the diphthong, while the single vowel is used in all forms having the same root at the end of the word, such as *septicemia*. The omission of *endocarditis, viridans* and *scarlatina* from the index reveals the level of content. The chapter on treatment is the best part of the book. Here the author writes vigorously and convincingly in evaluating the various therapeutic measures which have been proposed.

College News Notes

PROPOSAL OF NEW MEMBERS

The attention of all Masters and Fellows of the College is called to the By-Laws, Article V, Section 3 (c), Paragraph 2:

> "After 1931, a candidate for Fellowship shall be eligible only if already an Associate, except upon recommendation of the Committee on Credentials, by reason of very special qualifications."

Masters and Fellows who have candidates to propose for Fellowship should see that the forms are executed and filed in the office of the Executive Secretary of the College before December 31, 1931.

Attention is also called to the "Introductory Statement" appearing in the 1931-32 Directory of the College, especially paragraph 1 on page 22. Those Associates who have been elected since April 1, 1929, according to the By-Laws, must qualify for Fellowship within a period of from three to five years from the time of their election. Article VI, Section 3, of the By-Laws, provides that at the expiration of three years, an Associate shall be notified in writing of his eligibility for advancement to Fellowship during the next two years, providing he shall meet within that time the requirements necessary for Fellowship. If not elected to Fellowship within five years, his Associateship will automatically cease. In accordance with the above provisions, Associates eligible for proposal to Fellowship at the next Clinical Session have been notified.

Proposals for Fellowship now on file will be acted upon at a late autumn meeting of the Board of Regents. Proposals for Associateship will be acted upon during the San Francisco Clinical Session, due to the fact that they must first be approved by the Board of Governors before election by the Board of Regents. All proposals must be filed thirty days in advance of action.

1931-32 DIRECTORY

The Executive Secretary of the College completed the publication of a new directory of the Masters, Fellows and Associates during the past summer, and distributed a copy to all members in good standing on September 20. Although the contents have been limited to the most important biographical data, the volume has grown to one of four hundred and thirty-three pages, the compilation of which was a considerable task. Some members failed to return the biographical data sheets, in which cases their previous data were published. However, the great majority co-operated promptly, and a directory to a high degree inclusive and up to date has been produced. Members are requested to advice the Executive Secretary of any misprints, incomplete or imperfect data, so that corrections may be made in the next issue. This directory has become an important reference and guide for physicians and institutions all over the country.

Any member of the College in good standing who by any chance failed to receive the above mentioned directory during September is requested to communicate with the Executive Offices of the College. It has been determined that some copies were held at the Canadian Customs Office and not delivered. In a few other instances, copies may have failed to reach their destinations due to changes of address.

Dr. George E. Pfahler (Fellow), Professor of Radiology, Graduate School of Medicine of the University of Pennsylvania, attended the Third International Congress of Radiology held at the Sorbonne in Paris during the past summer. Dr. Pfahler presented a paper entitled "Roentgen Therapy in Carcinoma of the Breast—A Statistical Study of the Results in Over 1,000 Cases".

At the opening of the Congress, Dr. Pfahler presented an ivory gavel carved from the

tusk of a mastodon, imbedded for probably a million years in the ice of Alaska, to the President of the Congress, Dr. Antoine Béclère. In his presentation, Dr. Pfahler explained that not all in America is new and young, but that we too have our antiquities.

Dr. Edward A. Strecker (Fellow), Philadelphia, has been appointed Professor of Psychiatry in the University of Pennsylvania School of Medicine.

Among recent appointments in the Graduate School of Medicine of the University of Pennsylvania are the following:

Dr. Ralph Pemberton (Fellow), Professor of Medicine;

Dr. William D. Stroud (Fellow), Professor of Cardiology;

Dr. Truman G. Schnabel (Fellow), Assistant Professor of Medicine.

Dr. Carl V. Vischer (Fellow), Philadelphia, is the author of an article entitled "Student Instruction in the Medical Outpatient Department of Hahnemann Hospital of Philadelphia", which appeared in the September number of the Hahnemannian Monthly.

Dr. G. Harlan Wells (Fellow), Philadelphia, is the author of an article entitled "Care of the Heart in the Pneumonia Patient", which was published in the September number of the Hahnemannian Monthly.

Dr. Ralph Bernstein (Fellow), Philadelphia, discussed the Dermatologic Toxemias of Pregnancy in a contributed article which appeared in a recent issue of the Hahnemannian Monthly.

Dr. William B. Porter (Fellow) Professor of Medicine at the Medical College of Virginia, and Dr. Albert H. Hoge (Fellow), President-Elect of the West Virginia State Medical Association, were speakers at an alumni meeting of the Medical College of Virginia held at Charleston, October 12. Dr. Walter E. Vest (Fellow), Huntington, was Chairman of the Committee.

Dr. Porter and Dr. Hoge both addressed the Kanawha County Medical Society at Charleston, October 12.

Dr. Hoge addressed the West Virginia State Hospital Association at Huntington, September 21, and was also Toastmaster at their annual banquet.

Dr. Vest was elected President of the West Virginia State Hospital Association, September 21.

Dr. Henry M. Moses (Fellow), Brooklyn, N. Y., has been appointed Professor of Clinical Medicine at the Long Island College of Medicine.

On October 7, Dr. Moses presented a paper on "The Clinical Findings and Methods Used in the Diagnosis of Pulmonary Neoplasms" in a symposium on this subject at the staff meeting of the South Nassau Communities Hospital, Rockville Centre, New York.

Dr. John V. Barrow (Fellow), Los Angeles, lectured before the Hollywood Academy of Medicine, September 24; his subject being "Pathology and Treatment of Amebiasis, with Motion Picture Demonstrations of Organisms and Lesions".

D. R. Manning Clarke (Fellow), Los Angeles, has been elected Secretary of the Medical Section, California State Medical Association, for the year 1931-32. The next annual session will be held in Pasadena.

D. Samuel Ayers, Jr. (Fellow), Los Angeles, is co-author with Nelson P. Anderson and Esther M. Youngblood of an article entitled "Fumigation as an Aid in the Control of Superficial Fungus Infections" in the Archives of Dermatology and Syphilology, August, 1931.

Dr. Ayres is also co-author with Dr. Anderson of an article entitled "Dermatitis Medicamentosa Due to Ephedrine,' appearing in the August 15, 1931, issue of the Journal of the American Medical Association.

Dr. G. R. Maxwell (Fellow), Morgantown, W. Va., has been elected Chief of

Staff of the Monongalia County Hospital, Morgantown, for the year 1931-32.

Doctors Simon R. Blatteis, Frank B. Cross, Henry M. Moses and Philip I. Nash (Fellows) have been appointed Professors of Clinical Medicine, and Doctors Murray B. Gordon and Paul L. Parrish (Fellows) have been appointed Professors of Clinical Pediatrics, at the Long Island College of Medicine. These appointments carry with them seats in the administrative faculty.

Doctors E. G. Thompson, W. C. Colbert, C. H. Sanford and A. F. Cooper (Fellows) have recently been advanced to Associate Professors of Medicine at the University of Tennessee College of Medicine, Memphis.

Dr. B. M. Allen (Fellow), Wilmington, Del., addressed the 142nd annual session of the Medical Society of Delaware, October 14, on "X-Ray Diagnosis of the Chest with Special Reference to Fluid".

Dr. H. O. Colomb (Associate), formerly of Providence, R. I., has been appointed Clinical Director at the Central State Hospital, Pineville, La., as of October 1, 1931.

Dr. Solomon L. Cherry (Fellow), Clarksburg, W. Va., discussed a paper on "Dental Foci of Infection and their Systemic Effects" at a joint meeting of the Harrison County Medical and Dental Societies on October 1.

Dr. E. J. Engberg (Fellow), St. Paul, Minn., is the author of an article in Minnesota Medicine for October entitled, "Poliomyelitis in Minnesota".

Secretary Ray Lyman Wilbur, who is President of Better Homes in America, has recently appointed Dr. James M. Anders (Master) Chairman of the Better Homes Committee of Philadelphia for 1932. Dr. Anders has also been reappointed a member of the Board of Health of Philadelphia by the present Director of Public Health, Dr. Orlando H. Petty (Fellow).

At a Clinical Conference held under the auspices of the Staffs of the Leo N. Levi Memorial Hospital and Charles Steinberg Clinic, both of Hot Springs National Park, Ark., October 1, 1931, the following Fellows of the College took part:

Dr. A. G. Sullivan—"Etiological, Anatomical and Physiological Factors in Heart Disease";

Dr. D. C. Lee—"Laboratory Diagnosis of Syphilis with Demonstration";

Dr. Grayson E. Tarkington—"Dehydration in Epilepsy";

Dr. G. B. Fletcher—"Types of Paralysis: Points in Differential Diagnosis".

Dr. Mitchell Bernstein (Fellow), Philadelphia, was elected a member of the Board of Trustees of the Philadelphia College of Pharmacy and Science at its semi-annual meeting, September 28, 1931.

Dr. J. A. Myers (Fellow), Minneapolis, has been promoted from Associate Professor to Professor of Preventive Medicine at the University of Minnesota.

On September 22, Dr. Myers presented a paper before the annual joint meeting of the Medical Society of the County of Queens and the Queensboro Tuberculosis Association; on September 24, a paper before the general session of the 111th annual meeting of the Michigan State Medical Association; on October 2, a paper before the St. Joseph, Missouri, Medical Society and the Missouri State Tuberculosis Associationtion; on October 15, a paper before the Illinois State Nurses Association in Chicago; and on November 2, a paper before the Wisconsin Anti-Tuberculosis Association in Milwaukee.

Dr. William Devitt (Fellow), Founder and Directing Head of Devitt's Camp, Allenwood, Pa., on September 18, 1931, was honored by the local Rotary Club of Milton at a dinner and reception given as a "means of expressing to the widely known physician the measure of esteem and devotion held for him by his associates in the club, as well as by the thousands of residents of the Susquehanna Valley who have witnessed

his successful efforts at the Sanitarium that bears his name".

Dr. Robert G. Torrey (Fellow), has been appointed Professor of Principles and Practice of Medicine, succeeding the late Dr. L. Napoleon Boston, at the Woman's Medical College of Philadelphia.

Dr. J. M. Hutcheson (Fellow), Richmond, Va., and Dr. D. P. Scott (Fellow), Lynchburg, Va., addressed the Mecklenburg County Medical Society, September 15, on "Clinical Aspects of Coronary Thrombosis" and "Treatment of Nervous Patients", respectively.

At the Roanoke Meeting of the Medical Society of Virginia, October 6-8, 1931, Dr. D. C. Wilson (Fellow), Professor of Nervous Diseases at the University of Virginia, and Dr. Beverley R. Tucker (Fellow), Professor of Neurology and Psychiatry at the Medical College of Virginia, were speakers in connection with the mental hygiene symposium.

Dr. Horton Casparis (Fellow), Professor of Pediatrics at Vanderbilt University, Nashville, as guest speaker before the Virginia Pediatric Society, October 7, used as his title "Tuberculosis in Children: Prevention and Control".

Dr. A. L. Gray (Fellow), Richmond, Va., is President of the Virginia Roentgen Ray Club, which held its annual meeting at Roanoke in connection with the state meeting, October 7.

Dr. John E. Gardner (Fellow), Roanoke, Va., spent six weeks during the summer in special electrocardiographic work at the Johns Hopkins Hospital, Baltimore.

Dr. Beverley R. Tucker (Fellow), Richmond, attended the International Congress on Nervous Diseases in Berne, Switzerland, during the past summer.

Dr. D. T. McCall (Fellow), Mobile, Ala., recently addressed the Monroe County (Ala.) Medical Society.

Dr. Walter S. Leathers (Fellow), Nashville, recently addressed a conference of public health workers of Kentucky, Tennessee and Missouri.

Dr. Lea A. Riely and Dr. John E. Heatley (Fellows), both of Oklahoma City, Okla., gave addresses at the Osage County Medical Society's meeting on September 28, 1931—their subjects being, "The Clinical Aspects of Gall Bladder Disease" and "X-Ray Diagnosis of Gall Bladder Diseases", respectively.

Dr. Lewis J. Moorman (Fellow), Oklahoma City, Okla., has been elected Dean of the University of Oklahoma School of Medicine.

Dr. John M. Thorne (Fellow), Pittsburgh, addressed the McKeesport (Pa.) Academy of Medicine, October 26th, on "The Management of Cardio-Renal-Vascular Diseases".

On the recommendation of the Committee on Reorganization of the Sea View Hospital, Staten Island, New York, June 30, 1931, Doctor Louis Faugeres Bishop (Fellow), has been reappointed Consulting Cardiologist at Sea View Hospital.

Dr. Samuel E. Thompson (Fellow), Kerrville, Texas, has been re-elected President of the Southwest Texas District Medical Society.

Dr. Joseph McFarland (Fellow), Philadelphia, addressed the annual meeting of the Medical Society of Delaware at Wilmington on "Malignant Diseases of the Breast".

Dr. Francis E. Senear (Fellow), Chicago, presented a paper on "Modern Conceptions Concerning the Treatment of Syphilis" before the Peoria City Medical Society, October 6.

Dr. Carl F. Moll (Fellow), Flint, Mich., was installed as President of the Michigan State Medical Society at Pontiac, September 24.

Dr. W. Bernard Yegge (Fellow) of Denver addressed the Boulder County (Col.) Medical Society, October 8, on "Diagnosis and Treatment of Gastric Ulcer".

Dr. Henry F. Smyth (Fellow), Philadelphia, discussed "The Toxicity of Methyl Alcohol" before the annual meeting of the American Public Health Association at Montreal, September 7-10, 1931.

Dr. Carl R. Howson (Fellow), Los Angeles, addressed the Fresno County Medical Society, September 1, on the subject "Some Points in the Present-Day Treatment of Tuberculosis", and also the San Bernardino County Medical Society, October 6, on "The Future of Medicine".

Acknowledgment is made of the following gifts of reprints by members to the College Library:

Dr. George B. Fletcher (Fellow), Hot Springs Nat'l Park, Ark.—1 reprint;

Dr. Gustave P. Grabfield (Fellow), Boston, Mass.—6 reprints;

Dr. Samuel J. McClendon (Associate), San Diego, Calif.—4 reprints;

Dr. Aaron E. Parsonnet (Fellow), Newark, N. J.—2 reprints;

Dr. Meldrum K. Wylder (Fellow), Albuquerque, N. M.—1 reprint.

OBITUARY

DR. ROBERT GIBBS DOUGLAS

Dr. Robert Gibbs Douglas, Associate, Louisiana, died of malignant hypertension on July 23, 1931, aged 45 years.

Dr. Douglas was born in De Soto Parish, Louisiana, in 1885. He received his academic education at the University of Louisiana, while his medical degree was obtained from Tulane University of Louisiana School of Medicine in 1919. During 1920 his internship was spent in the City Hospital, St. Louis, Missouri. He returned home for a year and associated in practice with Dr. L. T. Baker of Dixie, Louisiana, where he remained until he became associated with the Highland Clinic in 1922. From that time until his death, Dr. Douglas confined his work to the study and practice of internal medicine. He endeared himself to his associates and to the community in general. At the time of his death he enjoyed a very large practice.

Dr. Douglas was a member and ex-President of the Caddo Parish Medical Society and a member of the Southern Medical Association, the Louisiana State Medical Association and the American Medical Association. He was elected to Associateship in the American College of Physicians during 1925.

He was a man of unusual ability, a gifted orator and a most lovable character, generous almost to a fault, never sparing himself in his endeavor to alleviate suffering. The Highland Staff has lost one of its most valuable coworkers and the community one of its most respected citizens.

(Furnished by T. P. Lloyd, M.D., F.A.C.P., Shreveport, La.)